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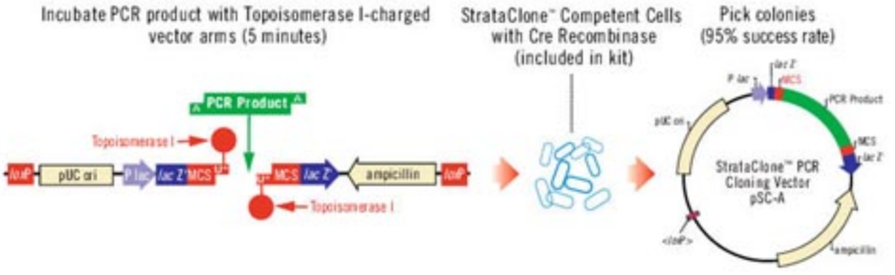

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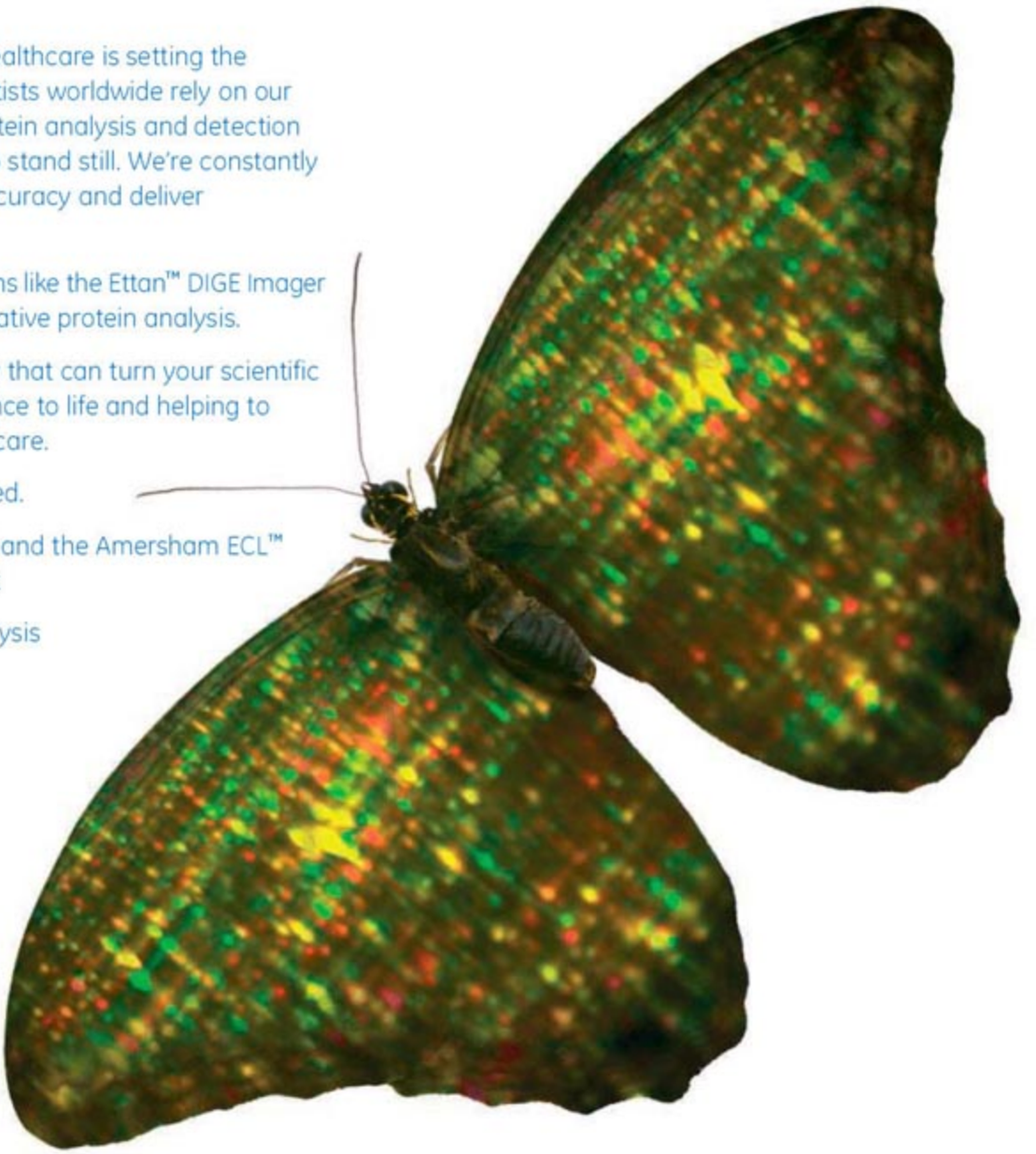


imagination at work

GE Healthcare Bio-Sciences AB, a General Electric Company.
Björkgatan 30, 751 84 Uppsala, Sweden.

GE08-06

Volume 315, Issue 5812

COVER

A protein growth factor (green) travels with the blood past a group of receptors anchored in the plasma membrane of a cell, as visualized by a new computer algorithm. The Gordon Research Conference on Visualization in Science and Education will be held 1 to 6 July 2007 at Bryant University, Smithfield, RI. The schedules for the 2007 Gordon Research Conferences begin on page 671.

Image: Graham T. Johnson/fivth.com

DEPARTMENTS

EDITORIAL

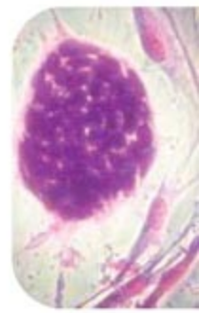
NEWS OF THE WEEK

NEWS FOCUS

LETTERS

BOOKS *ET AL.*

POLICY FORUM



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PERSPECTIVES

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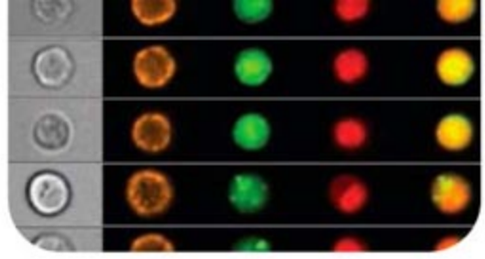

SCIENCE EXPRESS

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MICROBIOLOGY

Quantitative Phylogenetic Assessment of Microbial Communities in Diverse Environments

C. von Mering et al.

Analysis of microbial protein-coding genes from several ecosystems show that taxa prefer certain habitats and that the evolution is faster in some places than in others.

10.1126/science.1133420

PHYSIOLOGY

Regulation of *Drosophila* Life Span by Olfaction and Food-Derived Odors

S. Libert et al.

In flies, the ability of a severely calorie-restricted diet to extend life span can be partially reversed by exposing the flies to the odor of their main food, yeast.

>> *News story p. 584*

10.1126/science.1136610

IMMUNOLOGY

Autophagy-Dependent Viral Recognition by Plasmacytoid Dendritic Cells

H. K. Lee et al.

An unexpected function of autophagy (cellular self-digestion) is to unite RNA from infecting viruses with immune recognition molecules to trigger innate immune defenses.

10.1126/science.1136880

CLIMATE CHANGE

BREVIA: Recent Climate Observations Compared to Projections

S. Rahmstorf et al.

Sea level and global mean air temperatures have risen more since 1990 than climate models used in the IPCC predicted, and IPCC projections may underestimate future sea levels.

10.1126/science.1136843

TECHNICAL COMMENT ABSTRACTS

ECOLOGY

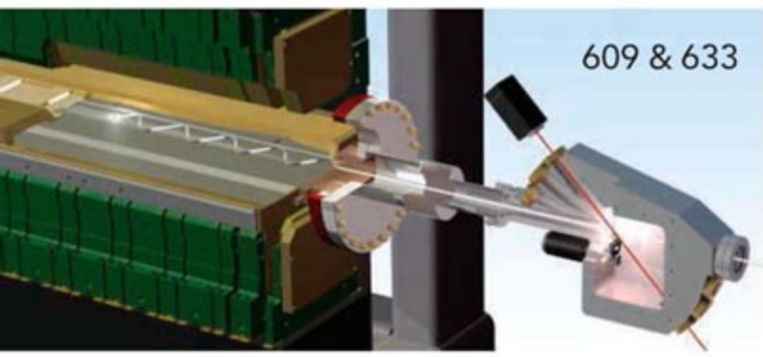
REVIEW

OCEANS

BREVIA

PSYCHOLOGY

In a Web-based survey, people conclude that anything that has feelings (such as hunger or pride) and the ability to act (such as communicating or showing self-restraint) possesses a mind.



REPORTS

MATERIALS SCIENCE

Adding barium titanate to tin produces a composite material that is stiffer than diamond, because the trapped inclusions have negative compressibility.

PHYSICAL CHEMISTRY

Average rates of electron tunneling in proteins, which seem to reflect the distance from donor to acceptor, are actually produced by multiple tunneling pathways.

CHEMISTRY

Because spectroscopy indicates that ultraviolet light damages DNA within 1 picosecond, the damage depends on the DNA conformation just before it absorbs the light.

CHEMISTRY

When light dissociates hydrogen gas, two dissociation pathways of opposite parity entangle, leading to correlations in the directions followed by the resulting proton, electron, and atom.

>> *Perspective p. 610*

CHEMISTRY

Femtosecond x-ray diffraction measurements show that as more electrons are excited, bismuth atoms in a lattice oscillate more slowly, softening the lattice as suggested by theory. >> *Perspective p. 609*

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new!

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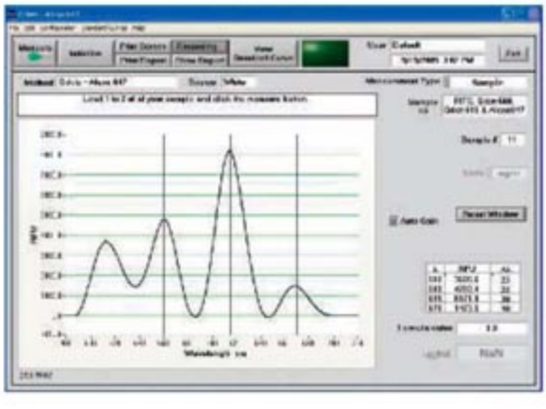

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REPORTS *CONTINUED...*

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Change of address: Allow 4 weeks, giving old and new addresses and 8-digit account number. **Postmaster:** Send change of address to AAAS, P.O. Box 96178, Washington, DC 20090–6178. **Single-copy sales:** $10.00 current issue, $15.00 back issue prepaid includes surface postage; bulk rates on request. The identification code for *Science* is 0036-8075. *Science* is indexed in the *Reader's Guide to Periodical Literature* and in several specialized indexes.

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New sleep drug may have fewer side effects than traditional medications.

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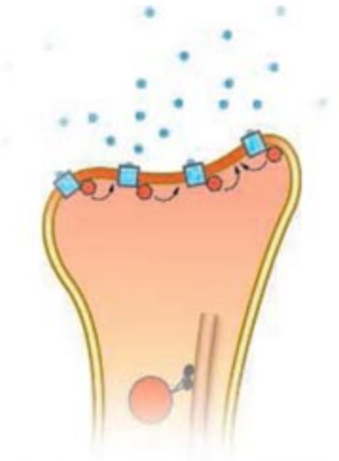
Catching some rays can boost the skin's defenses.



Local synthesis and kinesin-mediated delivery of PIP_3.

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T. Nakata and N. Hirokawa
Kinesins transport proteins and lipids necessary for neuronal process specification and maturation.

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Waiting for Congress to act.

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B. Benderly
Congress's failure to do its job has funding agencies and scientists pleading for pennies.

EUROPE: New EMBO Installation Grants
E. Pain
The European Molecular Biology Organization encourages expatriated scientists to set up research groups back home.

US: Working At—Oak Ridge National Laboratory
A. Fazekas
Researchers tell what it's like to work at the nation's largest science and energy laboratory.

GRANTSNET: February 2007 Funding News
J. Fernandez
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CREDITS (*SCIENCE CAREERS*): ANDY WRIGHT

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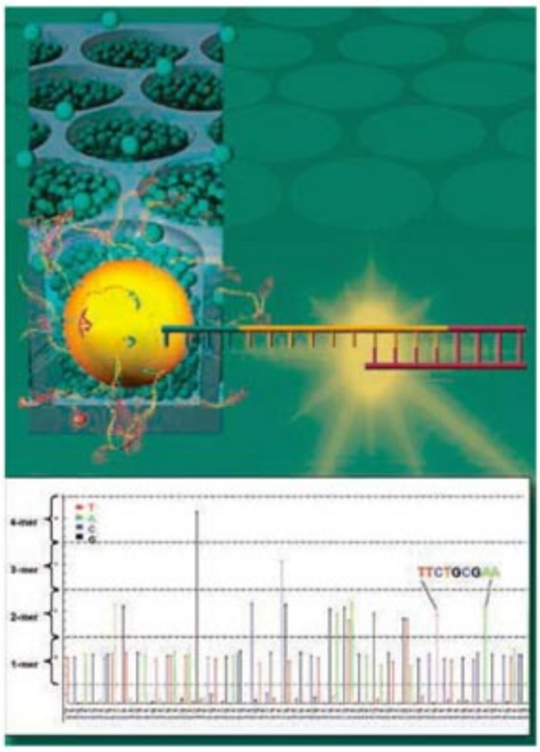

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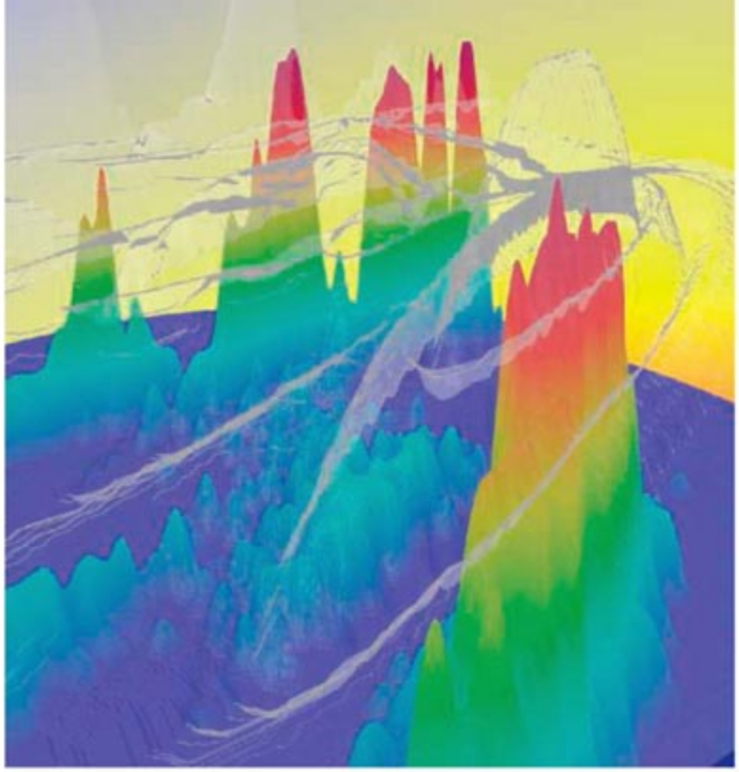


<< Broken Symmetry

Recently, active phase manipulation of ultrashort laser pulses has permitted researchers to direct the outcome of photoinduced molecular dissociations by exploiting quantum-mechanical interferences. **Martín *et al.*** (p. 629; see the Perspective by **Sanov**) show that even simple excitation of the H_2 molecule with high-energy, linearly polarized light can induce asymmetry in the trajectories followed by the formation of emergent proton, electron, and H atom products. Using high-level quantum mechanical calculations and precise experimental imaging techniques, the authors show that entanglement of two dissociation pathways of opposite parity leads to correlations in the directions followed by the three fragments.

Assessing Ocean Productivity

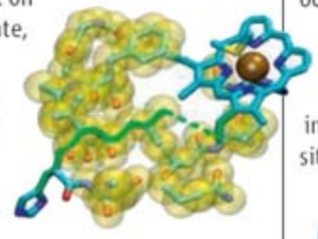
Approximately one-third of the ocean has abundant macronutrients but low iron concentrations, and it has been thought that this may limit productivity. As a test, iron was added to the surface ocean over large areas (tens to hundreds of square kilometers) in 12 experiments between 1993 and 2005. **Boyd *et al.*** (p. 612) summarize the results of these studies and discuss how iron controls the cycling of carbon, nitrogen, silicon, and sulfur, and influences bloom dynamics and ecosystem processes. Some of the highest productivity occurs in coastal upwelling zones; these provide about 20% of the world's fish harvest. Global warming, which should heat land masses more quickly than the ocean, could affect coastal wind regimes and hence upwelling. **McGregor *et al.*** (p. 637) construct a sea-surface temperature record for the northwest African margin, a major coastal upwelling region, for the past 2500 years. The surface waters have cooled in the 20th century there, which the authors interpret as a sign of more vigorous upwelling of cold, deep water, caused by stronger coastal winds. Increased upwelling in other coastal areas could impact fisheries and the carbon cycle.

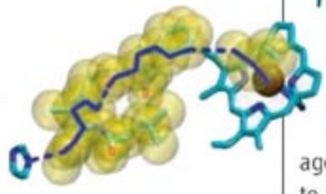
Getting Stiffed

Aside from their intrinsic beauty and value, diamonds are often considered the benchmark for properties such as hardness, stiffness, and thermal conductivity. **Jaglinski *et al.*** (p. 620) show that adding inclusions of barium titanate to tin creates a material with a viscoelastic stiffness higher than diamond. Barium titanate undergoes two phase transitions that change the crystal shape and volume. This leads to composites where the barium titanate has a negative bulk modulus, that is, when a force acts on the inclusions it causes a displacement in the opposite direction. When these composites are bent, the inclusions further stiffen the composite.

Electron Tunneling on Edge

In biological electron transfers, the structure of a protein between donor and acceptor sites should exert an effect on the overall transfer rate, but in many cases the data can be fit to simple models where the rate depends on distance. **Prytkova *et al.*** (p. 622) calculated rates for electron transfers in cytochrome b_{562} to surface-bound ruthenium centers, where the measured rates are known to represent electron tunneling. For seven cases where the rates appear to depend only on distance, multiple tunneling pathways through the heme edges are dynamically averaged. For two cases where the rates are much slower than the distance-dependence model predicts, tunneling occurs via a single pathway through an axial ligand. The authors show that the multi- versus single-pathway distinction accounts for the difference in tunneling rates in several other proteins, including some in photosynthesis.





Paired in a Flash

The most common form of ultraviolet (UV) photodamage to DNA dimerizes adjacent thymine bases, but the dynamics of this process have been challenging to measure. **Schreier *et al.*** (p. 625) use an ultrashort infrared laser probe to clock the dimerization rate in a single-stranded, 18-membered thymine oligonucleotide, and they find that bond formation is complete within 1 picosecond of UV light absorption. By comparing these results with quantum-yield measurements in double-stranded, mixed-sequence DNA, the authors infer that DNA photodamage occurs too quickly to involve significant conformational rearrangement. Thus, the damage may depend purely on the conformation in place at the instant of UV absorption. This insight should facilitate modeling of different sites' susceptibility to damage.

Metal in Motion

The structural consequences of electronic excitation in solids often occur on extremely short time and length scales. **Fritz *et al.*** (p. 633; see the Perspective by **Brock**) leverage advances in generation of short x-ray bursts to achieve real-time diffractive measurements of the lattice distortions in bismuth that follow electronic excitation by a near-infrared laser pulse. As the laser intensity is varied, the proportion of excited electrons increases. The bismuth centers oscillate at steadily decreasing phonon frequency, which reflects a softening of the lattice. The results agree with theoretical simulations and imply that this softening results from electronic coupling rather than from inherent anharmonicity of the phonon-mode potential.

Continued on page 571

CREDITS (TOP TO BOTTOM): MARTÍN *ET AL.*; PRYTKOVA *ET AL.*

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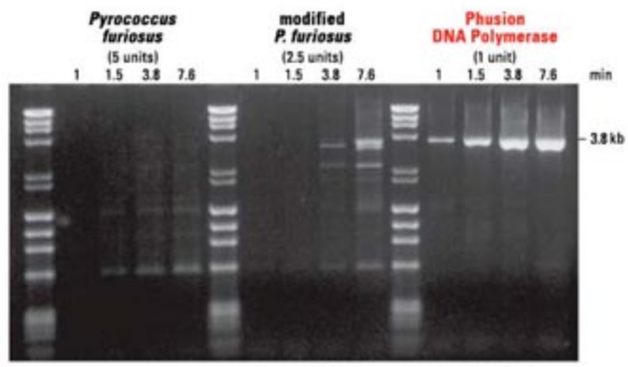

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Continued from page 569

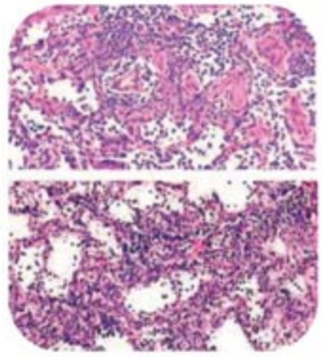
Community Effects of Climate Change

Most forecasts of ecological responses to climate change assume that these can be based on individual species tolerances for changing moisture or temperature regimes. **Suttle *et al.*** (p. 640; see the Perspective by **Walther**) challenge this assumption. In a 5-year experiment, they examined the consequences of alternative climate change scenarios in a grassland ecosystem in California, USA. Manipulation of rainfall over replicated 10-m diameter plots showed that higher-order species interactions dictate responses throughout the community. The effects on plant and arthropod abundance and diversity were the reverse of what would have been predicted based on individual species responses.

X-ing Out Tumor Suppression

Wilms tumor is a pediatric kidney cancer that can be inherited or arise sporadically. A small fraction of sporadic cases are caused by mutations in the WT1 gene on chromosome 11, which codes for a transcription factor regulating kidney development. **Rivera *et al.*** (p. 642, published online 4 January) now show that sporadic forms of Wilms tumor can also arise from mutations in a gene on the X chromosome, WTX. The function of the WTX protein is not yet known, but the gene's location on the X chromosome is of particular interest. Inactivation of most tumor suppressor genes requires two separate events or hits. Because humans carry only one functional allele of all X chromosome genes (in females one allele of each gene is silenced), the WTX gene presumably can be disabled by a single hit. The discovery of WTX suggests that X chromosome genes may play underappreciated roles in human cancer.

Limits on Viral Transmission



Transmission between hosts is a crucial choke point in viral evolution—viral fitness is measured by transmission. **Tumpey *et al.*** (p. 655; see the news story by **Enserink**) now show that one or two amino acid substitutions in influenza hemagglutinin that modify its sialic acid linkage specificity from mammalian to avian greatly reduce transmissibility of a recombinant 1918 influenza A virus in ferrets. This implies that hemagglutinin receptor specificity in this pandemic strain plays an essential role in influenza virus transmission.

Stopping Translation

Translation of a protein from its messenger (m) RNA is a complex and highly regulated process. Translation initiation requires many scores of factors and much more sequence information than merely the AUG "start" codon. The players involved in translation termination are not so clear. **Gross *et al.*** (p. 646) now show that the yeast RNA helicase Dbp5—which is known to have important functions in mRNA nuclear export and mRNP remodeling in the cytoplasm—plays a vital role in translation termination.

Quality Control in DNA Synthesis

A large variety of covalent modifications of histones, protein components of eukaryotic chromatin, play an important role in the regulation of transcription, and in DNA replication and repair. **Han *et al.*** (p. 653) and **Driscoll *et al.*** (p. 649) confirm that regulation of Ty1 transposition gene product 109 (Rtt109) is part of the DNA damage response during the DNA-synthesis phase of the cell cycle. It acts to acetylate histone H3 on lysine 56. Rtt109 functions in the same pathway as the histone chaperone Asf1, and is implicated in the stabilization of proteins at replication forks, possibly by coupling DNA synthesis to nucleosome assembly.

Mitochondrial Diversion and Aging

The protein $p66^{Shc}$ facilitates protein-protein interactions in growth factor signaling pathways. But mutations in Shc can enhance life span in mammals. This effect appears to depend on a different function of Shc whereby it exerts oxidoreductase activity in mitochondria and generates oxygen radicals that lead to cell death. **Pinton *et al.*** (p. 659; see the Perspective by **Hajnóczky and Hoek**) now show that the activity of Shc in the mitochondria depends on its phosphorylation by protein kinase Cβ and consequent binding of the prolylisomerase Pin1. This leads to a conformational change in the protein and to its accumulation in mitochondria. This signaling pathway could provide a target to help delay aging.

CREDIT: TUMPEY *ET AL.*

FOCUS ON CAREERS

Foreign Faculty Face Challenges

IN THIS ISSUE:

Many foreign-born scientists have made the United States their home because the country provides some of the best training and career opportunities worldwide. Learn how some researchers have survived, and overcome, the challenges facing foreign scientists working in the U.S. **Turn to page 695 for the full story.**

UPCOMING FEATURES:

March 2 — International Career Report: Science in Europe
April 6 — Careers in Cancer Research
April 20 — Postdoctoral Careers: Transferable Skills

Also available at www.sciencecareers.org ScienceCareers.org

Donald Kennedy is the Editor-in-Chief of *Science*.

Sustainability

THE THEME OF THIS YEAR'S ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE Advancement of Science (AAAS) focuses on sustainability and the need for scientific efforts to guarantee it. In next week's Editorial, AAAS President John Holdren will point out that human well-being has multiple dimensions and that the goal of sustainable well-being aims at improving all of them. His analysis focuses appropriately on how to manage our energy resources sustainably.

In its most straightforward formulation, sustainability would require that a resource be technically managed in such a way that its contribution to human welfare is conserved or improved for succeeding generations. But because the term has gained iconic status in the language of environmental conservation, it's hardly surprising that it now carries a lot of freight—in particular, a cargo of economic, social, and ethical assumptions and preferences, leading to different standards and expectations. In the interest of thinking about these before the forthcoming meeting, here are three sample sustainability scenarios we might explore.

First, the human population is growing, rapidly in some places (many developing countries) but unexpectedly slowly in others (much of Europe). If the objective of sustainability is to ensure the maintenance of available resource levels on a per-capita basis, then complex and very different utilization rules will have to be adopted by rapidly and slowly growing societies. Furthermore, societies of either kind will have to make difficult decisions about what resource levels are adequate. If each member of a generation at time t uses substantially more water per capita than is needed for his or her basic needs, then is it reasonable for that society to decide on a future water allocation that meets all of everyone's needs but no more? Can it then claim that it has managed the resource sustainably?

Next, complicated issues of transgenerational equity emerge from other scenarios. Suppose that at some time t, average per-capita access to some resource is adequate. In the $t + 1$ generation, average per-capita access is increased. But members of the top third in $t + 1$ receive substantially more than before, whereas those in the bottom third get less, and for some of them the allocation falls below the level of essentiality. Could such a society claim that the resource has been treated sustainably? Perhaps it would assert that wise conservation has produced a sustainable resource improvement. But most would argue that the failure of the transformation to manage reallocation equitably leaves it short of achieving a sustainable outcome.

Finally, there are other social and cultural challenges to sustainability that relate to rates of historical change. For example, societies often become accustomed to positive improvements in average welfare and are likely to insist that the upward trajectory continue. Suppose that the renewal rate of some resource is slightly higher than that of population growth, so that the annual increase in welfare on a per-capita basis has been a consistently positive number. Would the sustainability criterion be met by simply guaranteeing that generation $t + 1$ has the same welfare as generation t, or will those in $t + 1$ feel as though they have lost?

These scenarios suggest a problem with the concept of sustainability, which turns out not to be just about resource use, efficiency of utilization, and conservation. Instead, the term carries with it strong social, economic, and cultural attributes. Different societies will therefore create their own definitions of sustainability and their own criteria for achieving it, and they are likely to set about the task in their own ways. Articles in *Science*'s 2003 "State of the Planet" issues, now included in a book of the same title, have shown how small groups dependent on common-pool resources work out their own solutions and develop the means to enforce them.

Extending such successes to large-scale problems such as depletion of marine fisheries or global climate change is a difficult challenge. But more local successes have shown that social capital and broad participation in rule-making are important ingredients. In thinking about sustainability, prevailing economic, social, and ethical dimensions will be important factors in deciding what can work. Indeed, these are likely to dominate the technological aspects of resource management.

– Donald Kennedy

10.1126/science.1139909

EDITED BY GILBERT CHIN AND JAKE YESTON

PSYCHOLOGY

Calibrating Confidence

One of the challenges in reasoning by means of a deliberative and conscious process is the weighting of evidence that is reported by other humans. For people sitting as jurors in a trial, this translates into deciding whether to believe what a witness says. Previous studies have demonstrated that confidently uttered statements are believed more often and that being accurate on other issues, even those peripheral to the adjudicated question, is conducive to being believed.

Tenney *et al.* show an interaction between these parameters in mock trials of civil (car accident) and criminal (burglary) cases. Two witnesses were equally confident in asserting their recollections of how the accident had occurred, yet one was uncertain about other events that had taken place on that day whereas the other professed a complete and accurate recall. Subsequently, both witnesses were shown to have been correct about the weather conditions at the time of the incident, but both were also shown to have been in error in placing a personal appointment (entirely unrelated to the accident) on that same day. Although, as expected, the credibility of the supremely confident witness was rated higher initially, the less confident witness was regarded as being more credible after their fallibility had been revealed. — GJC

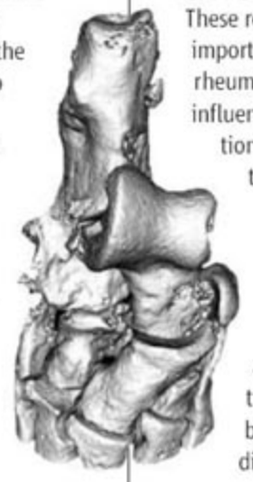
Psychol. Sci. **18**, 46 (2007).

BIOMEDICINE

Remodeling the Joint

Rheumatoid arthritis is a debilitating autoimmune disorder that is characterized by a profound remodeling of tissue architecture at the joint, which results, most notably, in a permanent loss of bone. Therapies that reduce joint inflammation have been somewhat successful in delaying the onset and progression of the disease, but they have not been able to reverse joint damage once it has occurred. Because the recovery of joint function in rheumatoid arthritis will probably require therapeutic approaches that trigger the formation of new bone, there is growing interest in understanding the molecular mechanisms that regulate bone remodeling within the joint.

Following up on previous evidence that identified the Wnt signaling pathway as a determinant of bone mass, Diarra *et al.* investigated whether manipulation of this pathway would affect joint pathology in mice overexpressing the proinflammatory molecule tumor necrosis factor–α (TNF-α), a widely used animal model of human rheumatoid arthritis. They found that the antibody-mediated blockade of Dickkopf-1 (DKK-1), which is an endogenous inhibitor of Wnt signaling, induced the formation of osteophytes (bone spurs) at the inflamed joints and also prevented the resorption of bone by specialized cells called osteoclasts. As was consistent with the mouse data, they observed that DKK-1 was expressed at aberrantly high levels in joint specimens from humans with rheumatoid arthritis and that in both species DKK-1 expression was induced by TNF-α. These results identify the Wnt pathway as an important regulator of joint remodeling in rheumatoid arthritis. Because Wnt signals influence both the formation and the destruction of bone, future therapies targeting this pathway could in principle be applied not only to rheumatoid arthritis, which is characterized by bone loss, but also to osteoarthritis and other diseases of the joint. — PAK



Bone erosion (pitted surfaces) in a mouse model of rheumatoid arthritis.

Nat. Med. 10.1038/nm1538 (2007).

ECOLOGY/EVOLUTION

No End of History

Teasing apart the relative roles of historical and contemporary climatic elements in determining species richness is one of the core quests of biogeographical research. Hitherto, success has been limited because of the correlative nature of models used. Rahbek *et al.* have developed a new class of spatially explicit, mechanistic models that use individual species distributions as a basic currency. Application of these predictive models to the distributions of birds in South America shows that current climate explains the distributions only of the most widespread species. Their results indicate that historical factors and community assembly processes may be more important in determining the distributions of species with narrower ranges; these species are, of course, generally of greater relevance in terms of conservation efforts. In turn, this adds to growing appreciation of the importance of incorporating longer-term considerations in conservation planning. — AMS

Proc. R. Soc. B **274**, 165 (2007).

PHYSICS

Looking for Lorentz Violations

Although symmetries underlie deep principles in physics (such as the conservation of momentum), ultraprecise measurements have revealed slight exceptions such as the CP (charge-parity) violation in some radioactive decays. Lorentz symmetry, which dictates that experimental measurements should not depend on whether the apparatus is moving at steady velocity or

CREDITS (TOP TO BOTTOM): PHOTOS.COM; DIARRA *ET AL.*, *NAT. MED.* 10.1038/NM1538 (2007)

standing still, is a cornerstone of special relativity. However, some researchers believe that there may be extremely small violations of Lorentz symmetry which, if measured, could provide tests of string theory and quantum gravity.

Experiments are now underway to search for Lorentz violations by trapping antihydrogen atoms. Altschul has calculated the properties of another possible experimental test known as vacuum Čerenkov emission. High-energy charged particles passing through matter give off light, such as the eerie blue glow of radioactive waste in a storage pool. If Lorentz symmetry is violated, particles moving through empty space may also emit Čerenkov light. Observing such emission would be extremely difficult but could serve as a valuable complement to the antimatter experiments. — DV

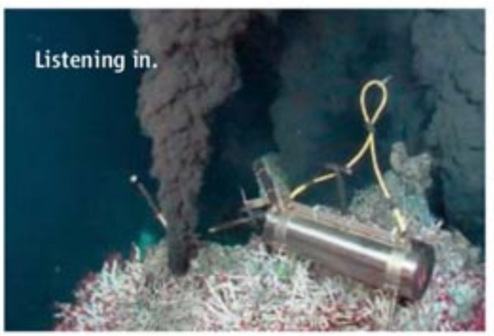
Phys. Rev. Lett. **98**, 041603 (2007).

OCEAN SCIENCE

Singing Vents

Mid-ocean ridges are dotted with hydrothermal vents termed black smokers. From these towers, dark streams of mineral-laced hot water bubble out to enrich the deep ocean and provide niche environments for many organisms. Little is known, however, about the patterns of hydrothermal flow from individual vents. As a means of monitoring the flow, Crone *et al.* have recorded the sounds of two black smokers, "Sully" and "Puffer," on the Juan de Fuca ridge 2200 m below the ocean surface. Submerged acoustic sensors provided close to 200 hours of recorded data. Both vents proved noisy, exceeding the ambient level by 10 to 30 dB. Broadband acoustic signals were measured at frequencies up to 500 Hz, possibly generated from a combination of volume changes in the flow, turbulence enhanced by fluid heterogeneity, and chimney vibration. Single tones sang out over the top, perhaps indicating resonant frequencies of the cavities. The authors speculate that such sounds could be used by organisms living near black smokers for navigation and to avoid the scorching water. — JB

PLoS ONE **1**, e133 (2006).



CREDIT: *ROV ROPOS* FUNDED BY THE W. M. KECK FOUNDATION/CRONE *ET AL.*, *PLOS ONE* **1**, E133 (2006)

CHEMISTRY

Resolving More with Less

Appending homogeneous catalysts to an oligomeric or dendritic support can concentrate active sites close to one another and thereby enhance the efficiency of cooperative processes. This approach has shown particular promise with the cobalt(III)-salen–catalyzed hydrolytic kinetic resolution of chiral epoxides, a highly selective reaction of interest because of the versatility of epoxides as precursors to pharmaceutically important targets. Mechanistic studies have indicated that two metal centers act cooperatively in this system, and catalysts with multiple Co-salen centers assembled as part of the backbone of a cyclic symmetrical oligomer have proven effective. Zheng *et al.* extend this strategy by preparing salen ligands substituted with cyclooctene and then using Ru-catalyzed ring-expanding olefin metathesis to create macrocycles with Co-salen moieties as pendant groups. The resulting compounds catalyze highly selective resolution of a range of alkyl- and aryl-substituted chiral epoxides at Co loadings as low as 0.01 mol %. The authors attribute the efficiency of this system to the spatial flexibility of the tethered metal centers. — PDS

J. Am. Chem. Soc. **129**, 10.1021/ja0641406 (2007).

PHYSIOLOGY

Obesity: in the Brain or the Gut?

Although some blame high-fat foods for the global spread of obesity, the mechanistic connection is not solid. The hormone leptin regulates body weight by binding to receptors in the hypothalamus and initiating signaling via JAK2, STAT3, and PI3K transducer molecules. JAK2 is a cytoplasmic tyrosine kinase and is the target of several regulators, including the SH2-B family. Mice whose SH2B1 is systemically knocked out become leptin-resistant and obese and develop type 2 diabetes. Ren *et al.* have found that if SH2B1 is restored specifically to neural tissues, the obese mice stop overeating, the hyperlipidemia is corrected, the leptin sensitivity is restored, and the obesity reverses. Nevertheless, therapeutic targeting of this signal may not be a simple matter if, as suggested by Ley *et al.* and Turnbaugh *et al.*, obesity can be mediated by members of the gut flora. It appears that obese mice and humans have a greater proportion of Firmicutes in their gut flora and that they extract energy from food more efficiently (because of the bacterial capacity for breaking down indigestible polysaccharides) than the Bacteroidetes group that dominates the flora of lean mice and people. Moreover, obesity in mice can be induced by infection. — CA

J. Clin Invest. 10.1172/JCI29417 (2007); *Nature* **444**, 1022; 1027 (2007).

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Creationism in Russia

A Russian court is scheduled to resume hearing testimony on 21 February in the country's first legal challenge to the teaching of Darwinian evolution.

Mariya Shraiber, 16, an 11th grader at public school No. 148 in St. Petersburg, has sued the Russian Ministry of Education and Science, claiming—on the basis of an obscure law governing political parties—that the school's biology textbook offends her religious sentiments because it does not allow for other theories, such as creationism. She also contends that the science in *The Origin of Species* is unproven and derived from Marxist-Leninist ideology.

The case—dubbed the "Monkey Process" by the Russian press as a nod to the Scopes trial—is being promoted by a maverick Russian public relations agent who set up a Web site called antidarvin.ru. Mariya's father Kirill, who is representing her in court, says his daughter does not belong to any particular faith.

The plaintiffs have the support of members of the Russian Orthodox Church, some of whom have regularly attended the court proceedings. Russian scientists are less enthusiastic. Nobel Prize–winning physicist Vitaly Ginzburg has characterized the lawsuit as "disgusting obscurantism and delirium."

Andrei Fursenko, the country's education and science minister, suggested last month in a radio interview that he is not averse to amending the textbook to include a variety of theories.

NET WATCH

Revising the Universe

In the 1920s, astronomers tussled over whether the universe has more than one galaxy. Less than a century earlier, the chemical composition of stars was unknown and, according to one philosopher, unknowable. Focus on how our understanding of the universe took shape at Cosmic Journey, a new history of cosmology from the American Institute of Physics (AIP) in College Park, Maryland.

Edwin Hubble and James Jeans with the 100-inch Mount Wilson telescope in California in the 1920s.

The exhibit traces intellectual developments from the ancient Greeks' Earth-centered universe to the modern idea that an enigmatic dark energy is speeding the expansion of the universe. Visitors can also follow the technological breakthroughs that opened up the cosmos, including refracting telescopes, spectroscopy, and radio astronomy. Biographical pages cover figures such as American astronomer Edwin Hubble (1889–1953), whose observations crushed the single-galaxy model of the universe and revealed that it was expanding. >> www.aip.org/history/cosmology

Plankton Art

At the turn of the 20th century, German naturalist and illustrator Ernst Haeckel captured the beauty of plankton and jellyfish (right). And when Monaco's Prince Albert I built the Monaco Oceanographic Museum and Aquarium in 1910, one of the designers transformed two of Haeckel's drawings, including one of an elaborate medusa, into chandeliers (below). The connection between Haeckel's creations and the Art Nouveau movement in architecture and design will be explored in an exhibit at the meeting of the American Society of Limnology and Oceanography next week in Santa Fe, New Mexico. On display will be jewelry, glassware, woodcarvings, paintings, photographs, and even a quilt—a rare treat for conventioneers tired of gazing at posters and vendor displays.

CREDITS: (TOP AND FAR RIGHT) GRAN/CONFRÉRIE DES GENS DE LA MER; (LEF, TOP TO BOTTOM): AIP; *ART FORMS IN NATURE: THE PRINTS OF ERNST HAECKEL*, PRESTEL-VERLAG, MUNICH AND NEW YORK COURTESY MUSÉE OCÉANOGRAPHIQUE DE MONACO

Slaves' camp. *Below*: Tromelin.

ISLE OF LOST SLAVES

On 31 July 1761, a French ship carrying 122 sailors and 60 slaves from Madagascar to Mauritius was wrecked off the tiny Indian Ocean island of Tromelin. The crew built a raft and sailed the 470 kilometers back to Madagascar, leaving the slaves with a 3 months' supply of food and promises that they would be rescued. Fifteen years later, a French ship picked up the only survivors, seven women and an 8-month-old baby. Before they were freed and lost to history, the women told their rescuers that they had kept a fire going continuously for the entire 15 years.

Last fall, 10 French researchers flew to the 1-square-kilometer island, where France maintains a weather station, and spent a month looking for traces of the slaves' ordeal. They found a wall of a building constructed from pieces of coral and sandstone, as well as some copper bowls and the bones of tortoises and fish. At a press conference in Paris on 17 January, the team also disclosed finding the oven in which the slaves had burnt pieces of the wrecked ship. From the layering of residues, they concluded that the fire had indeed burned until the rescue.

Expedition leader Max Guérout of France's Marine Archaeology Research Group says that the findings represent one of the rare instances in which "we have historical and archaeological evidence about slavery at the same time." More details are at www.archeonavale.org/Tromelin.

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In Print

A BRAIN REVEALED. Hendrikje van Andel-Schipper (above) was the world's oldest person and a minor celebrity when she died in 2005 at the age of 115. Now, many months after her decision to donate her body to research (*Science*, 9 September 2005, p. 1670), her name is at the center of a controversy.

On 23 January, anatomist Gert Holstege (left) of the University Medical Center Groningen (UMCG) in the Netherlands named Van Andel in a study published online by *Neurobiology of Aging*. Later that day, the center's governing board reprimanded him for revealing her identity. Although Holstege disagreed with UMCG's charge that he'd violated Van Andel's privacy, he asked the journal to retract the paper pending a resolution. The journal agreed.

Holstege says the medical center's suggestion to delete Van Andel's name makes no sense because her age and other details would be a dead giveaway. Besides, says Holstege, she had talked about her planned donation to reporters and "would have loved" the posthumous spotlight. "She was so sharp, I almost wanted her as a grad student," he said about Van Andel, whose brain he called comparable to that of someone in her 60s.

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IN THE COURTS

INVENTORS, KEEPERS. After a protracted legal fight with Duke University, physicist John Madey of the University of Hawaii, Manoa, has been reunited with a free-electron laser he built 2 decades ago. Madey plans to use the device to explore quantum-mechanical interactions between light and atoms and molecules.

Madey developed the laser at Stanford University and brought it with him to Duke in 1988. When Duke forced Madey out as head of the laser lab in 1997, he sued, claiming patent infringement. Duke, which kept the laser after Madey left a year later for Hawaii, claimed the right to use it for academic research. In 2003, a federal appeals court rejected Duke's argument. Madey and Duke reached a settlement last year, and the machine arrived at his lab in January. "I always knew it would happen," Madey says. "It was just a question of when."

HONORS

BIOCLOUT. Molecular biologist Nancy Ho of Purdue University in West Lafayette, Indiana, has won many accolades for her work on enzymes that make biofuels. But none matched her invitation to attend last week's State of the Union Address by President George W. Bush, who wants to boost biomass research funding. "I'm really very grateful for the honor," says Ho, who sat one seat away from First Lady Laura Bush. The diminutive (5 foot, 1 inch) scientist almost disappeared from view, however, when the TV cameras zoomed in on the honoree next to her, the 7-foot, 2-inch basketball player–turned-philanthropist Dikembe Mutombo. No problem, she says: The important thing is the newfound attention for her field.

MARINE SOS. A U.S. and a Chilean ecologist will share a $658,000 research prize from Spain's largest bank. Banco Bilbao Vizcaya Argentaria's foundation has recognized Jeremy Jackson of the Scripps Institution of Oceanography in San Diego, California, and Juan Carlos Castilla of the Catholic University of Chile in Santiago for lifetime achievements in marine conservation.

Jackson has studied the effects of the closing of the seaway that once joined the Pacific and Atlantic and has highlighted the devastating effects of overharvesting. Castilla has done experiments involving manipulation of rocky shore flora and fauna of Chile and tested "learning by doing" approaches to fisheries management.

<< Milestones

FORGOTTEN GENIUS. Percy Julian's synthesis in 1935 of physostigmine, used to treat glaucoma, has been called one of the 25 most important achievements in chemistry of the 20th century. In 1973, Julian became only the second African American to be elected to the National Academy of Sciences (NAS). But his accomplishments didn't stop racists from firebombing his home when Julian moved to the all-white Chicago suburb of Oak Park, Illinois, shortly after World War II. Although his neighbors decried the attacks, a greater deterrent may have been Julian's decision to spend night after night perched in a tree, shotgun in hand. Julian used the time to teach his then–10-year-old son about bigotry and intolerance.

Julian's story, "Forgotten Genius," will air 6 February on many PBS stations (pbs.org/wgbh/nova/julian). As Catherine Hunt, president of the American Chemical Society, said last week at an NAS screening of the show, "Percy Julian heard the word 'no' many times in his career and in his life, … and yet he persevered."

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VIROLOGY

From Two Mutations, an Important Clue About the Spanish Flu

HIV is lethal but not all that infectious; the common cold spreads easily but is fairly innocuous. The Spanish flu virus of 1918–1919 had the worst qualities of both, which is why it killed more people than World War I did. But although virologists have learned a lot about the combination of genes that made the virus so deadly, they could only speculate why it spread so easily.

No longer. A study published by *Science* this week (p. 655) confirms what many had suspected: A small change in the virus's hemagglutinin (HA)—a glycoprotein sitting on its surface by the hundreds—makes the 1918 virus more "avian" and unable to transmit between ferrets, even though it still sickened them. Those same changes in reverse may be what started the 1918 catastrophe—and what could kick off the next one as well.

"This is world news," says flu virologist Ron Fouchier of Erasmus Medical Center in Rotterdam, the Netherlands. "This answers the million-dollar question of how an avian virus can become transmissible between mammals." Still, exactly how the change in HA—which required just two point mutations—renders the virus impotent remains unclear, Fouchier says. Nor does it answer an even more urgent question: Could a similar set of mutations turn the bird flu virus H5N1, now devastating poultry in many countries, from an avian scourge into a human nightmare?

The HA in human flu viruses, such as the annual strains now sickening millions in the Northern Hemisphere, preferentially binds to a receptor on host cells that features a sialic acid bound to galactose through a linkage called α-2,6. This receptor predominates in both human and ferret airways. By contrast, avian viruses such as H5N1 have an HA with a slightly different shape that prefers to bind to a sialic acid linked to galactose through an α-2,3 link; these are in the majority in bird guts.

Based on that knowledge, researchers had suggested that the 1918 virus arose when an avian virus acquired mutations that gave it its predilection for α-2,6, thus becoming more "human" in nature. If so, reversing those mutations should be able to "avianize" the 1918 virus and make it unable to transmit among humans, says Terence Tumpey of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, the main author of the new study.

Small change. Two point mutations may have been enough to turn an avian virus into the 1918 flu, which killed more people than World War I.

So Tumpey, with colleagues at CDC and Mount Sinai School of Medicine in New York City, took the 1918 virus—which was resurrected over the past decade and is now the subject of intense study (*Science*, 7 October 2005, p. 28)—and made a few point mutations. One gave it an affinity for both the α-2,3 and α-2,6 receptors. One more switched its preference completely toward α-2,3.

When the researchers inoculated ferrets—the best animal model for human flu—intranasally with high doses of these two viruses, as well as the original 1918 strain, all three caused severe disease. But the ferrets to watch were those living in the cages next to the sick ones. With the original 1918 strain, they, too, became infected and got sick. With the strain that had a mutation that made it bind to both α-2,3 and α-2,6 receptors, transmission was inefficient; two out of three ferrets in adjoining cages developed antibodies, although neither became really ill. In the strain that bound to α-2,3 only, there was no transmission whatsoever.

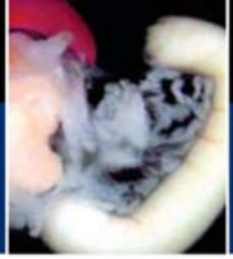
The study provides the first direct evidence that receptor preference is key to transmission, says virologist Mikhail Matrosovich of the National Institute for Medical Research in London. But why a few point mutations can have such a dramatic effect is less clear, he says. Although α-2,6 receptors predominate in ferrets, they also have α-2,3 receptors, as do humans; that's why the avianized virus was able to infect them. So why couldn't this strain make the jump to the next cage?

One clue lies in studies last year that showed that human cells with α-2,3 receptors occur primarily deep in the lungs, from where the virus may not so easily escape. α-2,6 receptors, in contrast, were found primarily in the upper respiratory tract. Another hint is that the ferrets infected with the avianized virus didn't sneeze, Tumpey says; it's not hard to see why that would reduce transmission in ferrets.

Several groups, meanwhile, are trying to find out if H5N1, too, could become a humanized virus through a few mutations in HA. Mutations in other genes are probably necessary as well, says Yoshihiro Kawaoka of the University of Wisconsin, Madison, and the University of Tokyo, and if humankind is lucky, researchers may discover that the combination of changes needed is unlikely to occur in nature. But in any case, knowing in advance what it takes would give scientists something to be on the lookout for in dead birds and human patients, Fouchier says—and ring the alarm bell if necessary.

–MARTIN ENSERINK

CREDIT: CORBIS



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PALEOANTHROPOLOGY

Small Brains, Big Fight: 'Hobbits' Called New Species

Gong! The latest round in the "hobbit" wars is under way. This week, a research team presented new data it says support the contention that a diminutive, small-brained hominid found on the Indonesian island of Flores truly represents a new species. The study, published online by the *Proceedings of the National Academy of Sciences* (*PNAS*), directly contradicts a paper published by skeptics last August in *PNAS*, which argued that the hobbit was a modern human with a severe deformity called microcephaly (*Science*, 25 August 2006, p. 1028). The new study compares the hobbit's puny brain to nine microcephalic brains and finds that the hobbit does not resemble them.

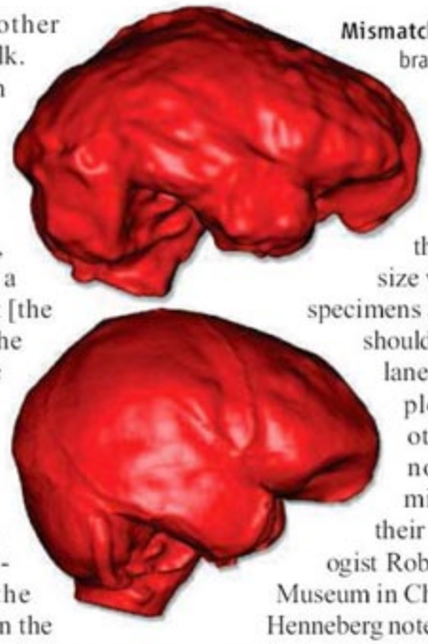
But although some researchers find the new work persuasive, scientists on both sides of the debate agree that it doesn't deliver a knockout punch and that only new fossil discoveries are likely to resolve the controversy. "This paper helps," says paleontologist Fred Spoor of University College London, "but we need another [hobbit] braincase to really settle it."

The team, led by anthropologist Dean Falk of Florida State University in Tallahassee, includes hobbit discoverers from Indonesia and Australia plus an international squad of radiologists. They had already compared the hobbit brain with one microcephalic brain and declared the two distinct (*Science*, 8 April 2005, p. 242), but critics found the single case unconvincing. So Falk and company created three-dimensional reconstructions of nine microcephalic and 10 normal human brains, using computed tomography scans of the interiors of the skulls. They looked for parameters with which to distinguish microcephalic brains from those of normal humans and found two: the width of the frontal lobes relative to the width of the cerebellum, and the extent to which the cerebellum protrudes from the back of the brain.

When the team added the hobbit to the analysis, it fell neatly into the normal human group. Moreover, two microcephalic brains that other researchers had claimed resembled the hobbit's (*Science*, 19 May 2006, p. 983) grouped with the microcephalic brains. "The most reasonable conclusion is that it represents another species of *Homo*," says Falk.

Anthropologist Ralph Holloway of Columbia University, who reported a comparison of six microcephalic endocasts at a meeting last March, says that the paper "does a good job of showing that [the hobbit] does not have the typical … microcephalic morphology." Nevertheless, Holloway remains troubled by what he sees as other signs of deformity in the lone hobbit braincase, including a pronounced flattening of the brain and abnormalities in the frontal lobes. "I would not throw out the pathology possibility yet. There is something about this brain that just doesn't seem right."

But a few skeptics want to throw the Falk paper out entirely. "It is incomplete, biased, and misleading," says anthropologist Maciej Henneberg of the University of Adelaide in Australia, a co-author of last August's *PNAS* paper. Henneberg argues that the Falk team's sample size was too small—at least 30 specimens are needed, he says—and should have included Australomelanesians, the aboriginal peoples of the region. On the other hand, the team should not have included four microcephalic children in their analysis, says anthropologist Robert D. Martin of the Field Museum in Chicago, Illinois.



Mismatch? The shape of the hobbit's brain (*top*) is different from that of an adult microcephalic.

Henneberg notes that Falk and the discovery team had argued previously that the hobbit sorts not with normal modern humans but with early hominids. Stay tuned: Falk says her next move is to add ancient hominids to her plot, and the discovery team hopes to dig again on Flores.

–MICHAEL BALTER

CREDIT: KIRK SMITH/MALLINCKRODT INSTITUTE OF RADIOLOGY

METABOLIC RESEARCH

Canadian Group Claims 'Unique' Database

No media splash greeted the completion of the Human Metabolome Project last week, although the sponsor boasts it is "the chemical equivalent of the Human Genome Project." The University of Alberta in Edmonton, Canada, announced that a small group of researchers with $7.5 million from the Canadian government has created a "comprehensive" database of human metabolites, calling it "the starting point for a new era in diagnosing and detecting diseases."

Since 2004, the scientists have assembled an inventory of 2500 molecules produced by metabolic reactions in the body's tissues and fluids. The Canadian project has been low profile until now, but the trumpeting of a completed "first draft" metabolome astonished some observers. Noting that the human genome was 90% complete when geneticists announced a draft, Gary Siuzdak of the Scripps Research Institute in San Diego, California, says, "I would be surprised if 2500 [entries] represents even 10%" of the human metabolome.

Still, the metabolome project leader, David Wishart, a biophysicist and computer scientist at the University of Alberta, says he's pleased. The product, described in a recent article in *Nucleic Acids Research*, is a free, public database (www.hmdb.ca) that some observers view as a solid first effort. Wishart and 39 co-authors—including five from the University of Calgary in Canada—describe the database as "unique."

The collection, which opened on 1 January, covers endogenous human metabolites, mainly from human tissue or gut bacteria. ▶

(A separate database covers drug metabolites.) Wishart says the project began with "text mining" of "dusty textbooks and obscure journals" to scoop up and validate previously identified metabolites.

Importantly, says Wishart, the collection provides more than 400 searchable "fingerprints," images of the atomic spectra of metabolites captured with nuclear magnetic resonance or mass spectroscopy. Users studying a specific metabolite can call up a "MetaboCard" that shows this fingerprint, if available, along with data on disease relevance, biofluid concentration, metabolic pathway, and many other topics.

Yet other metabolome researchers point out that there's a lot missing from the collection. Wishart and his colleagues narrowed their inventory to metabolites found at a concentration of 1 micromole or more. This simplified the task but eliminated tens of thousands of substances. Although Wishart says the present collection is 95% complete at 2500 entries, the group's paper acknowledges that if every small molecule in the body were to be included, "the number of compounds might exceed 100,000."

It's hard to define what's been left out, says Jeremy Nicholson of Imperial College London, head of an industry-backed project on potential toxicities in metabolic interactions—many of them difficult to detect (*Science*, 11 November 2005, p. 965). He views the database as "just a list" of detectable metabolites, although a useful list.

Ian Blair, a metabolomics leader and vice chair of pharmacology at the University of Pennsylvania, says the Canadian project made "quite a good start" on a complete database, although comparing it to the human genome is "over the top." Siuzdak, biochemist Julian Griffin of the University of Oxford, U.K., and several others are each leading independent efforts to build metabolome databases that could rival the Canadian effort.

Wishart acknowledges that the response to the metabolome's first draft has been "mixed." And he agrees that the estimate that the catalog is 95% complete is based on "a bit of a fuzzy number." But he considers the Canadian metabolome database the best and most user-friendly available. His big concern now is how to keep the project afloat after 2007, when government funding is scheduled to end.

–ELIOT MARSHALL

PHYSIOLOGY

Odor of Food Hastens Dieting Flies' Deaths

Put a fruit fly on a near-starvation diet, and it is likely to live much longer than its well-fed cousins. But if it smells food odors, some of the life-stretching effects of the diet disappear, researchers report in a study published online by *Science* this week (www.sciencemag.org/cgi/content/abstract/1136610). The finding adds to a growing body of evidence that an organism's perceptions of its environment can have a big impact on its longevity.

Molecular geneticist Cynthia Kenyon of the University of California, San Francisco, and her colleagues first sniffed out the link between life span and perception. In 2004, for example, Kenyon and postdoc Joy Alcedo reported that frying nematodes' olfactory neurons with a laser prolongs the worms' lives. Zapping certain taste neurons also promotes longevity, but destroying another one cuts survival.

To further probe the link between smell and life span, geneticist Scott Pletcher of Baylor College of Medicine in Houston, Texas, and colleagues placed fruit flies on an ascetic diet known as calorie restriction, which slashes food intake and can extend an animal's life by up to 50%. The researchers then planted tantalizing (at least to *Drosophila*) yeast paste in a screened-off end of the insects' home tubes; the bugs could smell and see the goodies but not eat them. Although the calorie-restricted flies lived longer than normal, they died sooner than similarly hungry insects not exposed to the yeast scent. The aroma had no impact on survival in well-fed *Drosophila*.

Unhealthy glow. An inserted gene, marked by fluorescence (green) and expressed in antennae, restored this fly's ability to smell and shortened its life.

Further support that the sense of smell affects life span came when the researchers measured survival in flies harboring a mutant form of the protein Or83b. The molecule helps direct odor receptors into position in the fly's olfactory organs, which are part of the antennae, and a faulty Or83b dulls the sense of smell. It also stretches fly longevity by up to 56%, the researchers found. Like many long-lived organisms, flies with mutant Or83b showed increased resistance to stresses such as starvation and a pure oxygen atmosphere. Restoring functional Or83b returned fly longevity to normal.

Many animals with extended life spans dial down insulin signaling (*Science*, 6 April 2001, p. 41). However, levels of fly insulinlike proteins didn't differ between the normal and Or83b-mutant insects, suggesting that odor exerts some of its longevity effects through another pathway.

The results "point out a central role for environmental perception in mediating life-history decisions," says Pletcher. The smell of food might cue animals to live for the moment because times appear to be good. But if nutrients are scarce, animals hunker down to await better conditions, boosting their resistance to stress and aging more slowly.

"It's incredibly exciting that the group has been able to show a link between the olfactory system and life span," says molecular geneticist Stephen Helfand of Brown University. The work reveals that "your brain has control over your life span."

The findings might also help clarify whether reduced food intake or another stimulus spurs calorie restriction's physiological changes. This study establishes that "some component of the response to caloric restriction is olfactory," says Kenyon.

So far, no evidence indicates that scent regulates vertebrate life span. However, says Kenyon, that the effect occurs in animals as distantly related as nematodes and flies indicates it could. Another unknown is whether other smells shorten longevity. And Pletcher notes that the presence of life-extending and life-shortening sensory neurons in nematodes "suggests that we could find odors that increase life span."

–MITCH LESLIE

CREDIT: S. LIBERT *ET AL.*, SCIENCE

2008 U.S. BUDGET

Ocean Research Gets a Modest Boost

It's more than a drop in the bucket. But the $40 million increase for U.S. ocean research proposed last week by the Bush Administration for 2008 falls far short of the torrent that two prestigious commissions said 3 years ago was needed to deal with declining fisheries, climate change, and a host of other problems in the seas.

The research bump is part of a $143 million spending boost for ocean projects in the president's upcoming 2008 budget request; Administration officials announced the increase in advance of the budget's 5 February submission to Congress. It covers four areas tagged as priorities in the next 2 to 5 years: natural hazards in coastal areas, basic research comparing marine ecosystems, new biosensors, and the role of Atlantic Ocean currents in rapid climate change. Most of the overall spending increase, if approved by Congress, would go to the National Oceanic and Atmospheric Administration (NOAA), although the smaller research pot would be split almost evenly between NOAA and the National Science Foundation (NSF), with the U.S. Geological Survey getting a tiny portion.

"This isn't good enough; it's off by a factor of 2," says Admiral James Watkins, a retired navy officer who co-chairs the Joint Ocean Commission Initiative (JOCI), a task force that lobbies for progress on recommendations made by the two commissions. In 2004, the U.S. Commission on Ocean Policy issued a report that called for a 5-year doubling, to $1.3 billion, of federal spending on ocean science. Still, some advocates see the Bush spending plan as a step in the right direction, and they also like an accompanying long-term research plan put together by an interagency group. "I think that's a very good sign for the future of the field," says Robert Gagosian, former director of the Woods Hole Oceanographic Institution in Massachusetts and an adviser to the U.S. Commission and JOCI.

CREDIT: R. LUMPKIN/NOAA/AOML

Charting the course. The proposed new research funding covers priority topics such as the Atlantic currents that influence climate change.

The report was drafted by the White House's Joint Subcommittee on Ocean Science and Technology, which began working on it in 2005. After a public meeting in April last year, the panel compiled 21 priority topics for ocean research that fit into six broad areas important to society, such as sustainable use of ocean resources and minimization of natural hazards. Agencies also identified near-term priorities in ocean research with the greatest impact and urgency, and suggested how much could be spent in each area.

The final figure "is in the ballpark" of what was proposed, says Julie Morris, head of the division of ocean sciences at NSF, one of the participating agencies. But the real surprise was the White House's willingness to fund any initiative in the upcoming 2008 budget, says Margaret Leinen, Morris's former boss, who last month stepped down as head of NSF's geosciences directorate. "Nobody was thinking that it wouldn't happen, but having it rolled out in '08 was very satisfying," says Leinen, now chief science officer for Climos, a greentech start-up company based in San Francisco, California (*Science*, 22 December 2006, p. 1847).

NOAA would get $123 million of the proposed $143 million in new spending, a 9.2% increase over the agency's request last year. (Its 2007 budget, like that of all domestic agencies, is still unresolved.) The new funds would cover $38 million for coral reef conservation and restoration of salmon habitat, $25 million to help end overfishing, and $40 million for research support, including $16.4 million for the Integrated Ocean Observing System, an embryonic network of sensors and buoys that has mostly been funded by earmarks. Although that amount would be far below the $70 million proposed for 2007 by a Senate spending panel (*Science*, 21 July 2006, p. 280), it is listed for the first time as a separate budget item, a step that observers say demonstrates the Administration's commitment to developing the system.

NOAA's share also includes $20 million ▶

Italian Center Back to Life

Italy's government is poised to rescue the Biomedical Research Center in Palermo. The project in regenerative medicine was jointly sponsored by the University of Pittsburgh and Palermo's ISMETT organ transplantation research center (*Science*, 27 October 2006, p. 577). More than 100 Italian scientists living abroad protested a government plan to withdraw support last year. Now the government has submitted a finance bill that would provide $340 million rather than the $410 million first proposed. The downsizing has forced a project review, but ISMETT says it hopes to begin recruiting staff later this month.

–FRANCESCO DE PRETIS

Stern But Kind at NASA

NASA Administrator Michael Griffin has found a new chief for the agency's beleaguered earth and space sciences program, insiders say. Griffin has been introducing S. Alan Stern, executive director of the Southwest Research Institute in Boulder, Colorado, around NASA's Washington, D.C., headquarters as a successor to Mary Cleave, who announced last September that she would leave this spring. Stern, a planetary scientist, is the principal investigator on NASA's Pluto–Kuiper belt mission and an advocate for lunar exploration—music, no doubt, to Griffin's ears. His challenge will be to preserve the agency's $5.5 billion commitment to science projects in the face of a flat budget and the growing appetite of NASA's human flight program. Stern did not return messages, and a NASA spokesperson declined comment.

–ANDREW LAWLER

More Direction for NIH

The freighterlike momentum of the National Institutes of Health (NIH) makes it notoriously hard to turn, but on 8 July the $28 billion agency will get a new steersman. Alan M. Krensky, a pediatric nephrologist and immunologist at Stanford University School of Medicine in Palo Alto, California, has been named director of the NIH office of portfolio analysis and strategic initiatives, a newly created post to help NIH Director Elias Zerhouni craft his agenda of high-priority programs known as the Roadmap. Krensky will also run a team that tracks spending across all NIH divisions and evaluates how well the agency hews to its goals.

Krensky, 56, already a consultant for the agency, says an important part of his job will be to align NIH spending with societal concerns such as the burden of specific diseases. His office will not impose priorities, he insists, but rather "facilitate" decisions by NIH institute chiefs.

–ELIOT MARSHALL

for priority research. NSF would get $17 million, and $3 million would go to the U.S. Geological Survey for mapping the sea floor and monitoring water quality. NOAA is still deciding which existing programs will receive the $20 million and how much would be extramural research, says Richard Spinrad, NOAA's assistant administrator for oceanic and atmospheric research.

And although the plan spells out NASA's critical role in ocean research, there was no mention of the agency at the 26 January press conference. "I'm shocked," says Len Pietrafesa of North Carolina State University in Raleigh, especially given last month's report from the National Academies' National Research Council highlighting the 30% decline in NASA's earth science budget over the past 6 years. Dan Walker of the White House Office of Science and Technology Policy, which worked on the research plan, says NASA is already contributing to ocean research.

Watkins says he will continue lobbying Congress to boost overall ocean funding to the level recommended in a recent report from JOCI. And he says he's optimistic that the new Democratic-led Congress will do better than its Republican-led predecessor. This week, for example, JOCI gave the nation a failing grade on funding for the field.

–ERIK STOKSTAD

With reporting by Jeffrey Mervis.

GEOLOGY

Indonesian Mud Volcano Unleashes a Torrent of Controversy

A mud volcano on Java that has destroyed four villages since it began erupting 8 months ago will likely continue spewing "for many months, if not years," according to the first published scientific report on the disaster. But experts are sparring over two points: whether the eruption was triggered by an earthquake or a gas well and whether anything can be done to stop it.

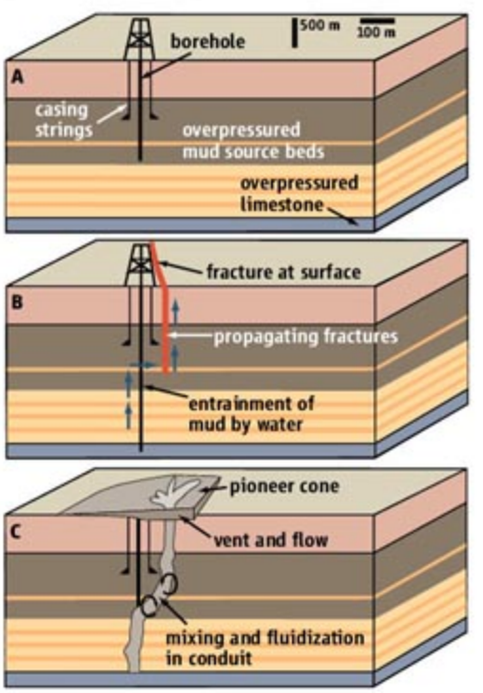
The volcano, known locally as "Lusi," roared to life on 29 May 2006 when steam and mud burst to the surface about 200 meters from an exploratory gas well near the coastal city of Sidoarjo, 700 kilometers east of Jakarta. The mud, up to 10 meters deep in places, has engulfed approximately 3.6 square kilometers and displaced more than 10,000 people.

Several geologists on the scene concluded that the rupture was related to the drilling (*Science*, 29 September 2006, p. 1865). But some Indonesian officials have pinned the blame on a magnitude-6.3 earthquake on 27 May 2006 that leveled parts of the ancient capital Yogyakarta, 280 kilometers southeast of Sidoarjo.

The new report discounts the earthquake scenario. After analyzing the site's geology, Richard Davies, a geologist at Durham University in the U.K., and colleagues argue that the drilling penetrated a highly pressurized and permeable limestone formation about 2800 meters deep. In the absence of a casing to protect the drill hole, fluid gushed back up, suffusing sediments and forcing mud to the surface through new fissures.

Davies's scenario, in this month's issue of *GSA Today*, has sparked a vigorous debate. It's "convincing," says Michael Manga, a geologist at the University of California, Berkeley, who has studied how earthquakes trigger volcanic eruptions. Manga says that in the Sidoarjo case, "the earthquake was too small and too far away."

Others are not so sure. The *GSA Today* report is "based on many speculations," says Adriano Mazzini, a geologist at the University of Oslo. The hypothesis relies on "unreleased geologic data," which Davies describes as drilling information provided to a co-author by a "reliable individual." His team also gleaned details from press releases and Web sites, but they have not visited the site, Davies says. Mazzini, on the other hand, went to Sidoarjo last fall to gather information and mud. "I'm working on a paper with real samples and real data," he says. But Mazzini is hedging his bets: "The earthquake could have contributed," he says; "it is also possible the drilling contributed."



Up and out. In a proposed scenario for Indonesia's mud eruption, a gas well is drilled far below a protective casing into permeable limestone, about 2800 meters deep (A). Pressurized fluid escaping from the limestone formation fractures overlying strata (B) and carries mud to the surface (C).

A lack of consensus has exposed a rift in the government. Aburizal Bakrie, minister of people's welfare, maintains that the mud volcano is a natural disaster and not the result of human negligence. His family's Bakrie Group conglomerate partly owns Lapindo Brantas, the drilling firm responsible for the hole. Last December, Indonesian President Susilo Bambang Yudhoyono ordered Lapindo Brantas to pay $420 million in compensation to local residents.

A more pressing concern is whether the flow can be stanched. "I would guess that stopping the eruption is impossible," says Manga. Mazzini and Davies agree. But last fall, William Abel, a Houston, Texas–based drilling expert who advises Lapindo Brantas, predicted that a relief well to intercept the original well 2100 meters down would allow engineers to plug the leak. However, work on the relief well was halted before it reached the target depth. After sinking more than $40 million into the relief well, "Lapindo Brantas has no more money, everybody has gone from the [drilling] site, and the rig is being taken down," says Rudi Rubiandini, a petroleum engineer at the Institut Teknologi Bandung who advises Indonesia's Ministry of Environment. Abel did not respond to a request for comment.

For now, the government is letting nature take its course. The mud, spurting at up to 150,000 cubic meters per day, is being channeled into a river that carries it to the sea. "It is difficult to predict how long the process of venting from the subsurface may continue if no action is taken," says Roger Sassen, a geochemist at Texas A&M University, College Station, who studies mud volcanoes. And the disaster may even widen: Davies predicts that the mud-laden region may subside or even collapse into caverns created by subterranean erosion, taking with it any hope the villagers have of ever returning home.

–DENNIS NORMILE

CREDIT: ADAPTED FROM R. DAVIES ET AL., GSA TODAY (FEBRUARY 2007)

DEVELOPMENTAL BIOLOGY

In Embryos, Pancreas and Liver Reach Full Size in Different Ways

As they morph from a clutch of cells to an elaborate system, organs stop growing. How they know when to do so has been an enduring mystery—and an increasingly important one as researchers pursue strategies aimed at regrowing tissue and even whole organs.

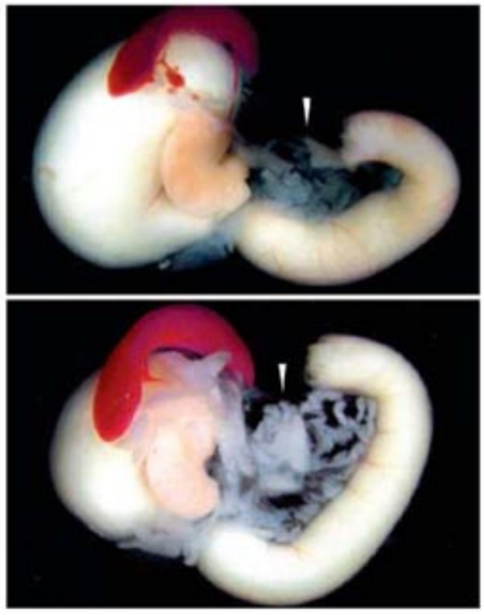
In a study published online this week by *Nature*, Douglas Melton, who co-directs the Harvard Stem Cell Institute in Boston, Massachusetts, and his colleagues suggest that the pancreas and liver have different strategies for determining their final size. The scientists report that destroying cells destined to become the pancreas leads to a proportionally smaller organ, whereas the liver reaches normal size despite the loss of starting cells.

Researchers knew that the pancreas has a lackluster capacity to regenerate in adults, but many "expected … there would occur compensatory growth" in embryos, says Palle Serup of the Hagedorn Research Institute, a division of Novo Nordisk, in Gentofte, Denmark. Melton's results indicate that powerful growth signals to the pancreas come from its own progenitor cells rather than from molecules elsewhere, says Serup. Still, some caution that the potency of external signals shouldn't be discounted. Pedro Herrera of the University of Geneva in Switzerland notes that a paper he co-authored last year showed that upregulating the molecule beta-catenin in mice produced a pancreas four times larger than normal.

In previous work, Melton's group had identified pancreas progenitor cells by a gene they expressed, *Pdx1*. In the new study, Melton and two members of his lab, Ben Stanger, now at the University of Pennsylvania, and Akemi Tanaka, used a clever technique to ablate *Pdx1*-expressing cells in mouse embryos. The scientists genetically engineered mice so that cells activating *Pdx1* would also turn on an inserted gene that encodes diphtheria toxin—unless the animals were given the drug tetracycline. To control the proportion of embryonic *Pdx1*-expressing cells killed by the toxin, they gave pregnant mice tetracycline at different times in their pregnancy. The researchers found that embryos whose mothers weren't given the drug until about 10 days into their development lost 60% of their *Pdx1* cells and their pancreases grew to 36% of the normal size. Even when the antibiotic was administered early and few cells were lost, the pancreas ended up smaller than normal.

In a second experiment, Melton's group began with mouse embryos lacking *Pdx1* altogether and injected them with different amounts of *Pdx1*-producing cells. They saw the reverse effect: The more cells expressing *Pdx1* the embryo received, the larger its pancreas turned out to be.

In the case of the liver, when Melton's group ablated at least 65% of early hepatic cells, organ growth was back to normal 4 days later. When it comes to regeneration, "the liver is a Ferrari," says Ken Zaret of the Fox Chase Cancer Center in Philadelphia, Pennsylvania.



Stunted. Killing pancreatic progenitor cells in the first days of the organ's development left a mouse with a pancreas (*top*, arrow) that weighed less than half as much as a normal mouse pancreas (*bottom*).

The new study "tells you something very fundamental," says Chris Wright of Vanderbilt University in Nashville, Tennessee. Like Melton, Wright believes that organs such as the blood, skin, and intestine contain stem cells that throughout life can proliferate and restock those tissues—as blood is replenished after a donation. But progenitor cells for other organs, including the pancreas, may naturally undergo only a precise number of cell divisions. That limit would set the size of the organ, and the cells would have more difficulty restocking tissue later in life. Melton wonders which genes "are setting this intrinsic limit" and is now planning to look for them.

–JENNIFER COUZIN

CREDIT: AKEMI JOY TANAKA

Sharing a Killer

The drive to share flu viral samples and information is gathering strength. On 26 January, the executive board of the World Health Organization (WHO) adopted a resolution that urges member states to "ensure the routine and timely sharing" of biological samples and genetic sequence data related to novel and potentially pandemic flu viruses, including H5N1, recovered from humans and animals.

David Heymann, who heads WHO's pandemic influenza efforts, says the resolution is "a first step towards developing the political will for free sharing of viruses and genetic sequences." The resolution, to be taken up in May by the WHO assembly, would formalize practices for sharing flu samples and information and could pave the way for proposals to transfer vaccine development technologies to developing countries. It is "essential" to compare sequence data from human and animal viruses, says Ilaria Capua, a virologist at Istituto Zooprofilattico Sperimentale delle Venezie in Legnaro, Italy. **–DENNIS NORMILE**

Hubble Loses an Eye

The main camera aboard NASA's orbiting Hubble Space Telescope has conked out, jeopardizing much of the work currently proposed for the aging scope. On 27 January, an electrical short in Hubble's Advanced Camera for Surveys (ACS), by far the most popular of the telescope's four instruments, killed the camera's ability to see deep and wide. "It's really a blow to Hubble science," says ACS principal investigator Holland Ford of Johns Hopkins University in Baltimore, Maryland.

Installed in 2002, the ACS is the workhorse for broad surveys that probe the structure of the cosmos. NASA engineers are pessimistic about the prospect for repairs, although a camera scheduled to be installed next year will be able to do some of ACS's work. **–ADRIAN CHO**

Asia Boosts Science Bonds

BANGKOK—Science chiefs of the Association of Southeast Asian Nations (ASEAN) member states have pledged to ease travel barriers and to intensify research collaborations. Meeting here last week, the officials agreed to ask their governments for collaborative flagship programs on disaster early-warning systems, biofuels, open-source software, and foods that prevent disease; details will be hammered out at a meeting in Vietnam in April. With ASEAN's main fund $4 million below its $10 million goal, supporters hope industry will pitch in.

–RICHARD STONE

Hot pots. Shards from Eilat Mazar's dig in Jerusalem are at the center of the heated debate.

CREDIT: COURTESY OF THE SHALEM CENTER

Judging Jerusalem

Has the palace of King David or Solomon been found? How big was their capital? New excavations and a bitter dispute over chronology put Jerusalem in the archaeological spotlight

PERCHED ON A NARROW AND WINDSWEPT hillside and remote from a major trade route, the Jerusalem of 3 millennia ago was ignored by Mesopotamian archives and rated only a brief mention in Egyptian chronicles. And despite a century and a half of excavations, archaeologists have yet to uncover incontrovertible evidence of the impressive capital described in biblical texts from which King David and his son Solomon presided over a wealthy empire from the Nile to the Euphrates.

Now, new excavation of a massive building in Jerusalem has intensified an acrimonious debate among archaeologists and biblical scholars over how to date and interpret finds from that early era. The excavating team, led by archaeologist Eilat Mazar of Hebrew University in Jerusalem, contends that the discovery bolsters the traditional view that a powerful Jewish king reigned from a substantial city around 1000 B.C.E. "The news is that this huge construction was not built by ancient Canaanites," she says, referring to the people who lived in the region before the Jews. And she goes a step further, arguing that the site is probably that of David's palace. Mazar says she will soon publish new radiocarbon dates to back up her claim. But other archaeologists are hesitant to assign the building's identity, and some question the dating. The city was "a typical highland village" until a century or so later, says Tel Aviv University archaeologist Israel Finkelstein, whose critique of ancient Jerusalem's influence has made him a target of scholarly ire (see sidebar, p. 591). That would make the biblical accounts wildly exaggerated, at best.

Academic spats about the dating of Iron Age cooking pots are not uncommon, but this one spills over into political and religious disputes as well. "You have similar situations throughout the ancient Near East, but they don't create the same level of emotion," says Lawson Younger, an epigrapher at Trinity International University in Deerfield, Illinois. Many nationalist Israelis and devout Christians are eager to prove the accuracy of the stories about David and Solomon, whereas some Palestinians suspect that Jewish-funded excavations aim at legitimizing Israeli control of a city that to Muslims is second only to Mecca.

The tension over Jerusalem's past was evident at recent meetings at Brown University and in Washington, D.C.,* where participants argued—sometimes loudly and angrily—about dating pottery shards, the influence of Jerusalem 3000 years ago, and the politics of funding digs. Resolving the contentious matter ultimately depends on refined dating techniques and a wider array of artifacts and sites. "What took place in the 9th and 10th centuries B.C.E. all depends on who you talk to," says Anson Rainey, a Tel Aviv University archaeologist. "It's all up in the air."

No simple site

Jerusalem sits squarely in the center of the Levant region, which connects Africa and Asia. But most of the ancient traffic of

* "The Jerusalem Perspective: 150 Years of Archaeological Research" at Brown University, 12–14 November 2006, and the American Schools of Oriental Research annual meeting, Washington, D.C., 15–18 November 2006.

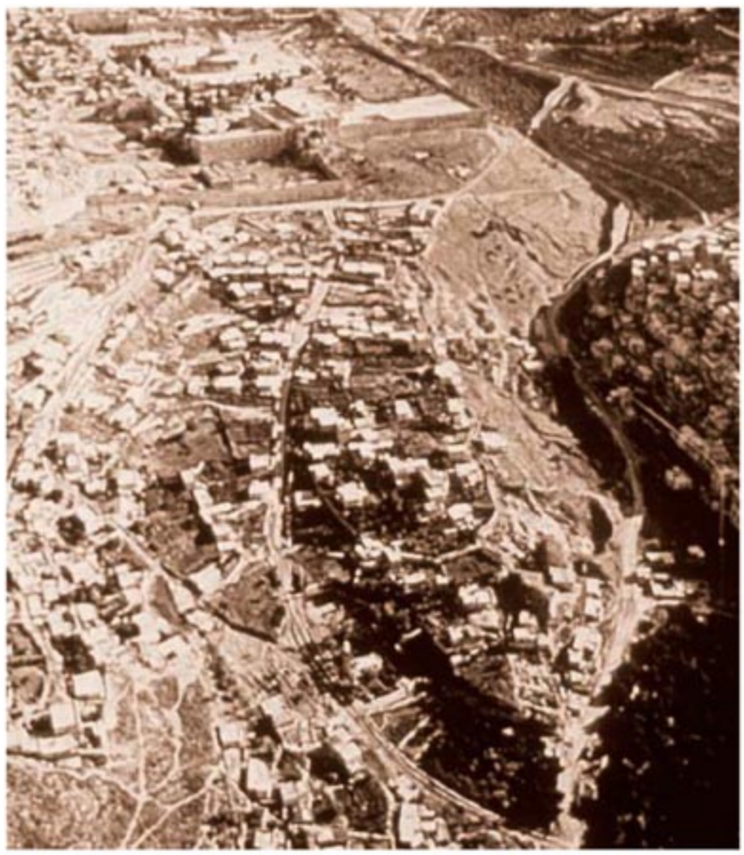
merchants and armies passed to the west, hugging the flat and well-watered Mediterranean coast (see map, p. 590). Deep in the hills between the Judean desert and the coast, Jerusalem is much younger than other sites in the region such as Megiddo or Jericho. Likely named for a Syrian god, the town is mentioned as early as the 19th century B.C.E. in Egyptian writings. Excavations show that 5 centuries later the site was fortified by a people called the Jebusites, who are associated with the Hittites of Anatolia.

According to biblical texts, Jewish tribes began to infiltrate the region by that time, setting up the southern kingdom of Judea and the northern kingdom of Israel and finally conquering independent Jerusalem under King David around what textual scholars estimate was the year 1000 B.C.E. David united the two kingdoms, and the Old Testament relates that his son Solomon turned the town into a showplace of the united monarchy, building several lavish buildings in Jerusalem and nearby cities. His empire collapsed shortly after his death, however, and the two kingdoms split. Jerusalem remained the capital of Judea for another 4 centuries but was destroyed by Babylon's King Nebuchadnezzar, who took many Jews into captivity.

There is, however, no direct archaeological evidence for the existence of the brief united monarchy and its empire. Decades of excavations in the City of David—located just south of the later city and just below what Muslims call the Harim al-Sharif and Jews dub the Temple Mount—provide an intriguing glimpse into the ancient town. But the data are difficult to interpret. "Jerusalem is not a simple archaeological site," explains Amihai Mazar, an archaeologist at Hebrew University. Stone was quarried and reused over millennia, erosion has taken a toll on the steep hillsides, and excavations since the 1800s have sometimes added to the confusion. And some of ancient Jerusalem is off-limits to archaeology because of political and religious sensitivities.

Now Eilat Mazar—a cousin to Amihai Mazar in the intimate world of Israeli archaeology—has wrapped up her second season of digging at what she argues is likely David's palace. She announced her initial finds last year, making headlines around the world. In 2005, her team started digging at the top of a large stepped-stone structure located at the narrowest point of the hill that makes up the City of David. That structure, an impressive 37 meters high, is made up of stone terraces that many archaeologists date to the 12th century B.C.E., prior to the arrival of the Jews.

Mazar, whose work is largely funded by a Jewish-American investment banker, has uncovered a large building on top of the structure, and she believes both structures were erected at the same time. "It's very clear this is one huge construction," she says. Her current excavation shows a building that covered as much as 2000 square meters. She adds that the complex appears to stand outside the original Jebusite city, and both the new building and more elaborate pottery left after the building's construction mark a clear break with the past. The site, Mazar notes, also matches biblical verses that talk of King David descending from his palace, indicating that it was on a high place.



David's city. Mazar's dig is south of the Dome of the Rock (*top left*) and in the neck of the teardrop-shaped hill that is the site of early Jerusalem.

CREDIT: CITY OF DAVID SOCIETY

Other archaeologists, although united in their conviction that Mazar's find is extremely important, are skeptical. Some maintain that it is more likely to be a Jebusite citadel rather than a palace built by David or Solomon, whereas others question whether the complex can ever be accurately dated, given its poor state of preservation. "The building is in bad shape, and so far she has not found a floor," notes Gabriel Barkai, an archaeologist at Bar-Ilan University in Ramat Gan who recently visited the site. That means "we have to rely on a chronological sandwich," adds Amihai Mazar, who also is familiar with the dig.

Time troubles

The key, then, is dating the elaborate pottery on the top and the coarse pottery on the bottom of that sandwich. And that is no easy matter, because no Jerusalem samples were radiocarbon-dated prior to Mazar's recent finds. Earlier archaeologists had not bothered to gather organic samples because radiocarbon dates for historical time periods were imprecise, with error bars of 1 or 2 centuries. Newer calibrations can sometimes pinpoint dates to within 50 years (*Science*, 15 September 2006, p. 1560), but it has taken time to adopt them. "Using radiocarbon in historical times is quite a young subject," Amihai Mazar says. As a result, archaeologists here have dated sites based solely on pottery styles.

Eilat Mazar dates the complex to about 1000 B.C.E., a date based both on new radiocarbon data as well as her interpretation of the pottery found at the site. Although many others see the plain ware as typical of the early Iron Age—that is, around the 12th century B.C.E.—she believes it was used in Jebusite Jerusalem right up to the time of the Jews' arrival. Mazar has also taken three new radiocarbon samples of bone and olive pits from under the building—the first samples in Jerusalem to be subjected to radiocarbon dating. These were associated with the plain pottery, and they date from 1050 B.C.E. to 1000 B.C.E., give or take a half-century—just prior to the time of David, she says. She also found a fourth sample at a later level associated with more elaborate pottery with Phoenician and Cypriot influence, in what appears to be an addition to the building. That material, which she believes was used by the early Jews in Jerusalem, dates to between 1050 B.C.E. and 780 B.C.E., with

one analysis pinpointing the most likely date to about 930 B.C.E.

The radiocarbon data have yet to be published, but even without them, Barkai, Amihai Mazar, and most other archaeologists who work in the area say that Jerusalem's pottery-based chronology is good enough, if inexact. Others—including Finkelstein—vehemently disagree and are agitating for a more accurate system that anchors the pottery firmly to radiocarbon dates. They point to the many carbon-14 samples obtained to the north of Jerusalem in the old kingdom of Israel. A team of Israeli scientists has taken more than 500 radiocarbon measurements from more than 150 samples from 25 sites, primarily in the north. Those results, says team member Ilan Sharon of Hebrew University, provide compelling evidence that the conventional chronology is off by a century, placing events earlier than they occurred.

After visiting Mazar's dig this week, Finkelstein says the building may be as late as the 6th century B.C.E. If so, the picture of a 10th century united monarchy with monumental buildings falls apart. "There is no evidence for a glamorous capital of Jerusalem," he maintains. For him, the biblical accounts of Solomon's golden age were written centuries later, with an eye to contemporary politics rather than historical accuracy. Archaeologist Rafi Greenberg of Tel Aviv University adds that the countryside around Jerusalem lacks the villages one would expect to support a substantial town or city. "In the late 8th century B.C.E., there was rapid development, but we find zilch before then," he says. "Jerusalem is the worst possible site for agriculture and can only sustain—optimistically—about 500 people."

But those who back the conventional chronology dismiss this view as uninformed at best and foolish at worst. They say the early Jewish city was well-fortified, included monumental buildings and structures, and operated as an important regional power, if not as the large empire imagined by biblical writers. Mazar's find provides additional evidence of a significant city, says Jane Cahill, an archaeologist based in Houston, Texas, who is associated with Hebrew University and has dug in the City of David: "The stepped-stone structure is the most impressive monument in Israel until classical times." Cahill estimates that 10th century B.C.E. Jerusalem, extending over 12 acres or 5 hectares, was home to 1200 to 1500 people—small compared to contemporary cities such as Babylon, but large for the Judean highlands of the era.

Finkelstein's and Greenberg's views are angrily challenged by many Jerusalem archaeologists, who accuse them of taking an extreme "minimalist" view that the Bible offers little or no guidance for historians. "I believe in the accuracy of the biblical accounts—I don't think they invented King Solomon," declares Barkai. Cahill takes Finkelstein to task for mixing northern and southern pottery, which she says are culturally distinct. She also notes that Cypriot and other foreign pottery in Eilat Mazar's building tie it neatly to the 10th century B.C.E.

All in the Family

As a young archaeologist digging in the City of David, an ancient site just south of walled Jerusalem, Eilat Mazar unearthed huge pottery vessels buried just before Nebuchadnezzar, the king of Babylon, destroyed Jerusalem 2500 years ago. The pots were stamped with ancient Hebrew writing—and she could read it. The moment crystallized her sense of belonging to the contested city. "This was my language, not some foreign tongue, and it speaks to who I am today and where I was born," Mazar says.

Today, at 50, Hebrew University archaeologist Mazar is wrapping up a second season uncovering what could be the most significant archaeological find in Jerusalem's history: the palace of the king who, according to biblical texts, united the ancient Israelites (see main text). For her, excavating in Jerusalem is more than a purely scientific endeavor; it is also a family affair, heavily steeped in the complex history, politics, and religion of the place.

Mazar grew up in a secular home which nonetheless included innumerable editions of the Bible and commentaries on it. She still prizes the Bible once owned by her grandfather, Benjamin Mazar, a renowned archaeologist and Polish emigrant. "He was my main teacher relative to thinking and methodology, and how to combine historical sources with archaeology," she says. Mazar's attachment to those sources is legendary; she is fond of saying that she digs with one hand while holding the Bible in the other. But she insists her attachment is purely scholarly: "I've never felt a religious connection to my work."

Palace puzzle. Mazar at her Jerusalem complex.

CREDIT: KATHERINE AMRANI

The connection, however, is deeply felt. She was outraged in 2000 when she learned of building activities on the Temple Mount, an important site that is called the Harim al-Sharif by Muslims, who have controlled it for most of the last millennium. Mazar formed a committee to protest destruction of antiquities on the site but was disappointed when Israeli authorities took little action. She adds that her protest is not religious or political: "Islamic monuments are being destroyed too. This is a site important to the world's cultural heritage."

But some Palestinians find that hard to square with Israel's own policy about excavations. Hamed Salem, a Birzeit University archaeologist who lives near Mazar's current dig, explains that "the Palestinian view is that this dig is illegal" because the territory is considered occupied by the Israelis under international law. "Archaeology is supposed to be neutral," says Salem. "The conclusions which come out of this excavation will not be on a purely scientific basis." And a few Israeli archaeologists fear that her funding, which comes through Jerusalem's Shalem Center, a Jewish research institute, creates at least the appearance of a nationalist rather than purely scientific endeavor.

Mazar, however, insists that she is not digging to prove anyone's preconceived notions. "I'm trying my best," she says, "to keep an open mind." **–A.L.**

And other archaeologists note that the lack of evidence for neighboring villages could be due to their establishment on exposed bedrock, leaving few traces behind.

When pressed, however, Jerusalem archaeologists admit that their dating remains maddeningly imprecise. "We don't have firm dates until we get to [Assyrian King] Sennacherib in 701 B.C.E.," says Rainey. "The question is whether radiocarbon dating can solve anything." Barkai is deeply skeptical. "Given the margin of error, radiocarbon allows everyone to argue the position they already hold," he says. "Carbon-14 is like a prostitute." But others acknowledge that resolving the conflict ultimately depends on more samples to provide absolute dating—which means firmly anchoring the pottery to radiocarbon dates. "There is no other way," says Ayelet Gilboa, a Haifa University archaeologist who is part of the radiocarbon team.

Amid the dispute, which at times appears bitter and deeply personal, there are signs of a convergence. "We all agree Jerusalem was not a major city, it was a small town," says Amihai Mazar. Adds Herschel Shanks, editor of *Biblical Archaeological Review*: "It wasn't this big wonderful thing … but a capital of a few small villages." Cahill agrees that although Jerusalem was "a splendid city" compared to other highland towns, it was "a poor and sad place" compared to the metropolises of its day. For his part, Finkelstein acknowledges that Jerusalem may have expanded starting as early as 970 B.C.E.—in the late 10th century and only 50 years later than the position held by Cahill.

Divisive agendas, however, are inherent in the debate. Eilat Mazar's work is done in partnership with the Ir David Foundation, which says it is dedicated to "strengthening Israel's current and historic connection to Jerusalem." Mahmoud Hawari, a Palestinian archaeologist at Oxford University, warns that "you cannot avoid a political and ideological motivation in discussing David and Solomon. Biblical archaeology has tried to prove that link and has served modern Zionism." But Mazar defends her funding. "I'm doing pure research, and no one tells me what to do or write."

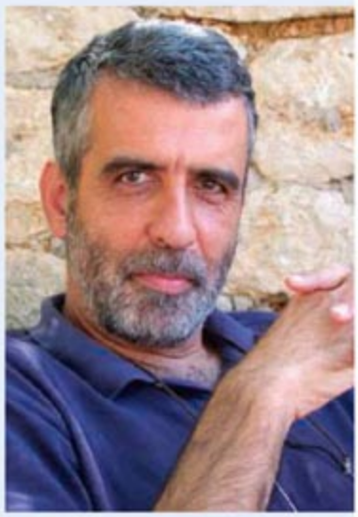
Ultimately, better data from tools such as radiocarbon dating could provide a clearer picture of the ancient city. Gilboa believes a wave of data could lead to "a new and more vigorous biblical archaeology" that uses the Bible as a guide rather than diktat. That approach might allow archaeologists to shed more light—and generate less heat—on Jerusalem's Iron Age predecessor. **–ANDREW LAWLER**

CREDIT: JEREMY JOSEPHS

Holy Land Prophet or Enfant Terrible?

By suggesting that biblical figures such as David and Solomon were, at most, unimposing tribal chieftains ruling from a nondescript hill town, Israel Finkelstein has made himself a lightning rod. His controversial views about what took place 3000 years ago touch a nerve among many nonacademic Israelis, evoking angry letters in the country's newspapers from people questioning his patriotism.

It's an ironic position for a self-described "mainstream Zionist" who grew up in the first Zionist settlement in what is today Israel. The 57-year-old Tel Aviv University professor is the ringleader of a small number of researchers who dispute the way archaeologists date their finds in the area around Jerusalem (see main text). If these scholarly renegades are correct, then the military exploits of Joshua, the brave deeds of David, and the wisdom of Solomon may be no more historical than the medieval tales of King Arthur. Finkelstein says he wants to bring modern techniques to a rather fusty field that in his view depends too heavily on biblical texts—but his critics suspect his real goal is to grab the media spotlight.



Bad boy. Finkelstein is nearly as controversial as his theories.

Finkelstein insists he didn't go looking for trouble. He recalls a "perfectly normal" childhood in which he pestered his parents to take him to archaeological sites. And until the 1980s, he published papers backing the conventional archaeological chronology. He used pottery to date sites and assumed that the biblical texts provided a good road map for excavators. But that changed in the early 1990s, when Palestinian uprisings forced him to give up digs in the highlands north of Jerusalem. He moved to the lowland city of Megiddo, 150 kilometers north. Famed as the New Testament site of Armageddon, the ancient town was the home of an impressive gate and palace long considered Solomonic.

At Megiddo, Finkelstein sensed something fundamental was wrong with the dating, so he plunged into carbon-14 sample gathering, which at the time was rarely used at historical sites. "Radiocarbon opened the way to put ourselves on solid ground, free of all these arguments about the Bible," he says. At about the same time, a team of researchers from several Israeli universities independently began to conduct carbon-14 analyses. They say they have good—although not conclusive—evidence that the conventional dating in the north of Israel is off by a century. That would mean the Megiddo structures were built after Solomon—and after the biblical united kingdom—by local rulers.

The radiocarbon data fueled Finkelstein's interest in, and suspicions of, the biblical accounts. After in-depth study, he says he decided that much of what was written about the era of David and Solomon was done long after the fact for political purposes. That conclusion led him to question archaeological work in Jerusalem, where he has never excavated. And it also created a political and religious as well as an academic firestorm.

In the wake of the Holocaust, Israeli leaders, although secular, drew on the stories of fierce fighters and wise kings to create what Finkelstein calls "the myth of the new Jew, the fighting Jew." His critics—at meetings, in books, and in newspapers—railed against him as irresponsible and sensationalistic. "He's a radical, politically and otherwise," says William Dever, an archaeologist emeritus at the University of Arizona, Tucson. Dever has worked in Israel for 50 years and has known Finkelstein since he was a high school student. "Even then, he was insufferable," Dever maintains. "For him, this is a kind of game and an ego trip. … He has become too outrageous."

Jane Cahill, an archaeologist associated with Hebrew University, agrees that Finkelstein "requires his detractors to carry the burden of proof" and that he "resorts to bellicose rhetoric." Finkelstein dismisses the criticism as the last gasp of a conservative establishment that is suspicious of new techniques, fears undercutting the Bible, and is jealous of someone who works well with the media; Finkelstein is a frequent television commentator, and his book sales are brisk. But he admits that he can come across as something of a bully. "I have a big mouth, and I know how to protect myself—I'm streetwise."

But even Finkelstein feels the heat sometimes. At a recent conference in Washington, D.C., he purposely avoided a session on 10th century B.C.E. Jerusalem. "It's not good for my health," he explained with a hint of embarrassment. "I have daughters, and I have to try to survive." **–A.L.**

CANCER RESEARCH

Probing the Roots Of Race and Cancer

African-American women are more likely to develop aggressive breast tumors than are Caucasians. Funmi Olopade is trying to understand why

CREDIT: DAN DRY/UNIVERSITY OF CHICAGO MEDICAL CENTER

CHICAGO, ILLINOIS—The breast cancer patients Olufunmilayo Olopade saw as a resident at Cook County Hospital in Chicago reminded her of home. In her native Nigeria, as in the Chicago, Illinois, neighborhoods served by Cook County, the women she saw with breast cancer were often poor, black, unusually young, and very ill. Chicago was a world apart from the Lagos that Olopade had left behind in 1982. She had come to the United States to collect a brother who had dropped out of graduate school. Instead, she wound up settling in this snowy city. Working at Cook County, she became intrigued by the cancer parallels: Often the tumors were aggressive, the patients were young, and, in racially diverse Chicago, they were disproportionately of African descent. "What is this about?" she remembers thinking.

Twenty-five years later, that question anchors Olopade's expansive and frenetic efforts to unravel the disparities of breast cancer. It's long been known that black women, although less likely to suffer from the disease than whites, are far more likely to die of it, a difference traditionally attributed to lack of access to health care. But Olopade and a number of other scientists are finding something else: In more than a dozen studies, they've documented that breast tumors in African-American women tend to be more aggressive, less responsive to treatment, and more likely to strike before menopause than breast tumors in whites and other ethnic groups. The differences persist even when statisticians adjust for every variable they can think of, from body weight to education to the cancer treatment given.

Still, the "science of disparity," as Olopade likes to call it, remains on the periphery of oncology research. Oncologists worry that by focusing on it, they'll be perceived as dismissive of the very real gulf in access to care. And they're generally reluctant to seek physiological distinctions between races. "It's such a contentious issue, and it causes people so much stress to conclude there may be a difference" in biology, says Wendy Woodward, a radiation oncologist who treats breast cancer at M. D. Anderson Cancer Center in Houston, Texas. She recently reported that even when black women with breast cancer receive the same treatment as whites in clinical trials, their chance of developing incurable metastases is about 20% greater.

Olopade, a commanding presence with a radio announcer's voice, was one of the first to call attention to these differences in the late 1990s. Today, she treats patients at the University of Chicago (U Chicago), where she also runs a 12-person molecular biology lab and participates in a vast, multimillion-dollar study of the effects of stress on breast cancer susceptibility in mice and people. Her network is growing. Last year, she inspired the founder of Crate and Barrel, the home furnishings retail chain, to help raise $1 million for the university's breast cancer research efforts. In 2005, the MacArthur Foundation rewarded her with one of its $500,000, no-strings-attached "genius" grants.

Olopade, who goes by the nickname Funmi, is using her MacArthur money to trace the biology of disparity to where its roots may lie, in Africa. Her efforts intensified after tumor samples she collected 3 years ago from women in Nigeria and Senegal revealed an even higher rate of aggressive disease than in African-American women—suggesting that genetics may partly explain the difference.

Troubling differences

Studying disparity was not what Olopade first had in mind. When she arrived at the University of Chicago, she focused on the genetics of leukemia and lymphoma and later on breast cancer. Two genes that conferred a high risk of breast cancer, *BRCA1* and *BRCA2*, had recently been discovered, and Olopade established a clinic to counsel and treat women with *BRCA* mutations and other high-risk characteristics.

Many of the young black women in her clinic who had not inherited *BRCA* mutations, Olopade noticed, nonetheless seemed to develop a form of breast cancer that closely resembled that seen in *BRCA1* carriers. Known as estrogen-receptor-negative (ER-negative) breast cancer, these tumors are not fueled by estrogen and do not respond to drugs such as tamoxifen and raloxifene that cut off their supply of the hormone. They also tend to metastasize and spread more quickly than ER-positive tumors.

As a breast oncologist, "you really get hit in the face with the relatively unique or different cancers that are afflicting women of African background," says Lisa Newman, director of the breast care center at the University of Michigan, Ann Arbor. Like Olopade, she was struck by the young age of many of her black patients—and indeed, studies have shown that 31% of African-American breast cancer sufferers are under age 50; the comparable figure for white Americans is 21%. Furthermore, systematic surveys have recently confirmed the anecdotal evidence gathered by physicians such as Olopade and Newman: Nearly 40% of breast cancer cases among African-American women are ER-negative, compared with 23% of cases among whites.

As technologies advance, clinicians are identifying cancers by more precise signatures. Last June, for example, a team of U.S. and Canadian researchers published results in *The Journal of the American Medical Association* from the Carolina Breast Cancer Study, which examined the prevalence of different breast cancer subtypes among 496 breast cancer patients. The researchers were particularly interested in a high-risk "basal-like subtype." These "triple-negative" tumors—negative for estrogen receptors, progesterone receptors, and human epidermal growth factor receptor-2 (HER2)—tend to spread quickly. And because they don't respond to targeted new drugs, they can be hit only with traditional chemotherapy.

Breast Tumors: More Common in Whites, Deadlier in Blacks

	Breast cancer incidence	Survival*	Under age 50	ER-negative	High grade
Caucasians	134/100,000	90%	21%	23%	41%
African Americans	118/100,000	77%	31%	39%	57%

* Five years after diagnosis.

Triple-negative tumors, it turns out, are also unusually prevalent in young African-American women. Of the 97 premenopausal African Americans in the Carolina Breast Cancer study, 39% had this subtype. Among postmenopausal African Americans, the number was 14%, whereas in the 300 non–African Americans, regardless of age, it held steady at 16%. "The question is how much is nature, how much is nurture, how much is something else?" says Lisa Carey, a breast oncologist at the University of North Carolina, Chapel Hill, who helped conduct the study.

Back to Africa

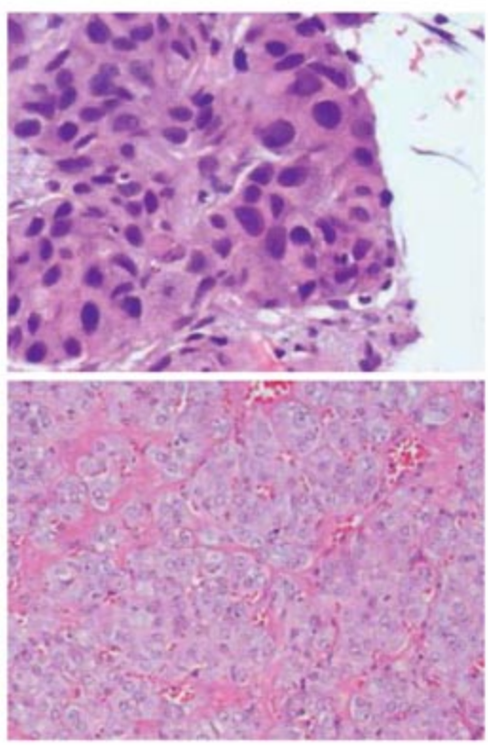
"I started off thinking that it was all genetics," explains Olopade. On a frigid December day in Chicago, she's striding between campus buildings after a meeting with members of the National Institutes of Health. Three officials are in town for the day to evaluate the university's $9.7 million Center for Interdisciplinary Health Disparities Research, which Olopade helped launch with her next-door neighbor and U Chicago colleague, biopsychologist Martha McClintock, and social scientist Sarah Gehlert. Olopade, in a black suit with thin white stripes and a black coat with fur trim, shows no signs of fatigue despite having left the hospital at midnight the night before, after admitting two seriously ill African-American breast cancer patients. Word among her colleagues is that she rarely sleeps.

She's also one of a tiny handful of breast cancer experts turning to Africa to help explain racial disparities. After confirming that fewer than 10% of the women in a group of patients from Nigeria had inherited a *BRCA* mutation, Olopade found that a startling 77% of 378 samples from Nigeria and Senegal were ER-negative. This contrasts with 39% in African Americans and 23% in Caucasians. Although many of the African women were young, and younger breast cancer patients are more prone to have ER-negative tumors, the numbers were still off the charts. "This just blew us away," she says. Those results, which Olopade and her colleagues presented at a cancer meeting in 2005 and are readying for publication, led her to believe that aggressive breast cancers in blacks are driven by an interplay of genes and environment.

These days, Olopade is joined in Africa by Newman, who is recruiting breast cancer patients in Kumasi, Ghana, in collaboration with Ghanaian investigators. "A lot of the slave[s] came through" Ghana before traveling to America, notes Newman, who hopes that by comparing samples from Ghanaian women with those from African Americans and whites, she'll develop a better understanding of what's driving aggressive, ER-negative disease.

Like others in the field, Newman has encountered concern about turning back to "an era of practicing race medicine, where you get one type of care if you're black and another if you're white," she says. Newman, who's African-American herself, decries that view. "We're talking about a cancer-control issue," she says. "Getting a better sense of the hereditary issues … has implications for women worldwide."

But in tackling the genetics behind breast cancer disparity, researchers must also address what race, a crude construct, really means. "Race is not a scientific category," says Harold Freeman, a cancer surgeon and medical director of the Ralph Lauren Center



Triple jeopardy. Breast tumors negative for three key markers (*top*) are tougher to treat than the triple-positive variety (*bottom*); in one study, 39% of young African Americans had triple-negative tumors, compared to 16% of Caucasians.

SOURCE: AMEND *ET AL.*, *CANCER RESEARCH* 17 66 (2006); IMAGE CREDIT: MARIA BRAMAN/UNIVERSITY OF MICHIGAN

for Cancer Care and Prevention in New York City. While he praises Olopade's work, he is skeptical about performing research on populations whose distinctions he considers socially determined. And even if biological differences are relevant, Africans and African Americans "come from the most genetically diverse continent in the world," says Lovell Jones, who conducts health disparities research at M. D. Anderson Cancer Center. It's important to specify race according to place of origin and not rely on vague identities, he says. He's beginning a study of Nigerian immigrants in Houston, their relatives who remain in Africa, and African-American women, to determine whether susceptibility to breast cancer differs as a way of estimating the importance of environmental factors.

Olopade is taking a closer look at environment herself. Several years ago, she launched another Nigerian project, now funded by the U.S. National Cancer Institute, for which she's recruiting 2000 women, half with breast cancer and half without. She and her colleagues are gathering information about their environment, family history, and, if relevant, their tumors. Members of her lab are also now studying African-American breast tumors for patterns of methylation—regulatory alterations in DNA—in the *BRCA1* gene. Olopade wonders whether an altered form of the normal *BRCA1* gene could account for more aggressive tumors in some blacks.

DNA methylation can be brought about by environmental factors, agrees Lieutenant Colonel Larry Maxwell, director of the gynecologic disease program at Walter Reed Army Medical Center in Washington, D.C. His work focuses on uterine cancer, in which black women more often fare worse than whites. Maxwell is studying methylation patterns to discern differences in the tumors of African Americans and Caucasians.

In the Chicago health-disparity center to which Olopade devotes a slice of her time, another environmental driver may be emerging. Co-Director McClintock has shown that when rats are socially isolated early in life, increasing stress and vigilance and prompting immune system changes, they develop breast tumors 40% earlier and four times more often than do animals housed in groups. The isolated rats also display larger, more aggressive tumors.

Now the center is recruiting hundreds of African-American women with breast cancer in Chicago to begin assessing whether social isolation and stress-hormone levels predispose to cancer. "The whole idea is to elevate it to a science," says Olopade of disparity research.

Branching out

The field seems to be gaining momentum. In October, the American Association for Cancer Research (AACR) hosted 30 researchers in Philadelphia, Pennsylvania, to discuss the science of cancer disparities and plan a large meeting on the subject for the end of 2007, which Olopade will co-chair. "It's been understudied," admits Margaret Foti, chief executive officer of AACR, of disparity science.

Sleuthing for answers. Olopade, with one of her patients, is adamant that the black-white survival gap isn't due only to inadequate access to health care.

Kathy Albain, a breast oncologist at Loyola University Medical Center in Maywood, Illinois, has been poring over data from decades of clinical trials. Among 19,400 patients, 12% of whom were African American, differences in survival by race emerged for ovarian, breast, and prostate cancers. Despite uniform treatment, blacks fared worse, on average, than whites, even after adjusting for differences in tumor type and other factors. But no comparable survival differences surfaced for other cancers, including lung cancer, leukemia, colon cancer, and multiple myeloma. "There must be something else going on pertaining to molecular biology, pharmacogenetics, hormonal issues," says Albain, who presented her most recent data, an in-depth analysis of more than 6000 breast cancer patients, at a meeting last December in San Antonio, Texas. She and her colleagues are looking more closely at a number of other variables in the different cancers, from white blood cell counts to drug doses.

Even as disparity research draws more scientists, it remains a touchy topic. It's "a very loaded area," says Timothy Rebbeck, who studies prostate cancer disparities at the University of Pennsylvania. "You can imagine saying, 'There is a genetic basis to health disparities.' It's something you have to say very carefully so it doesn't get misinterpreted."

Some cancer researchers also worry that disparity research could lend support to racial stereotyping. "If you listen to some folks, … it sounds like they're talking about blacks having weaker genetics," says Otis Brawley, deputy director of the Emory Winship Cancer Institute in Atlanta, Georgia. Brawley believes that studying the science of disparities has distracted from focusing on disparities in treatment and access to care. "I'm not the only one who feels this way," he adds, although "I may be the loudest."

Olopade the straight talker responds forcefully to such criticisms, arguing that the aggressive disease she so often sees is not due only to poverty and lack of access to care. And she has strong defenders, especially among colleagues such as Rebbeck, who has collaborated with her for many years. "She's very outspoken and forceful and direct in a good way," he says.

Olopade says that her patients are the ones who really remind her how broad disparities research should be. Visiting the hospital room of a 50-year-old African-American breast cancer sufferer, who initially declined treatment and whose triple-negative disease has spread through her chest, she touches the woman gently on the shoulder, inquires about her family, and asks her to please listen to her doctors. "It keeps me thinking—that woman, why is she in the position she's in?" she wonders later. "If I don't have the experience of seeing patients like that, who walk in, and I studied disparities," she says, "I would never get it."

–JENNIFER COUZIN

CREDIT: DAN DRY/UNIVERSITY OF CHICAGO MEDICAL CENTER

SCIENCE EDUCATION

States Urged to Sign Up for a Higher Standard of Learning

Legislators, expert panel join the chorus of those seeking a voluntary national standard for science and math in U.S. schools

Mississippi education officials patted themselves on the back in 2005 when state-administered tests showed that 53% of the state's 8th graders were proficient in math—a jump of 14 percentage points in the 3 years since federal mandates for improving school performance went into effect. But a few months later, a nonbinding, nationwide evaluation found that only 13% of that cohort were proficient, ranking Mississippi last on the country's math scorecard. The discrepancy—a product of standards that reflect the state's low expectations for student achievement in math—earned Mississippi a "cream puff" award from an education journal published by Stanford's Hoover Institution.

The tremendous variation in what a state teaches and the way it measures how well children are learning has triggered a move for national standards and assessments in elementary and secondary school science and math education. Last month, two legislators long active in education reform—Senator Christopher Dodd (D–CT) and Representative Vernon Ehlers (R–MI)—introduced a bill to create and implement a set of voluntary national standards in math and science. A week later, a panel reporting to the policymaking body that oversees the National Science Foundation went further, calling not just for national standards but also for national assessments of student achievement in science and math and national certification for teachers in those fields. "Currently, we have states adopting less-than-rigorous standards to game the system," says Shirley Malcom, co-chair of the National Science Board's Commission on 21st Century Education in Science, Technology, Engineering, and Mathematics and head of education and human resources programs at AAAS (publisher of *Science*). "As a nation, we need to drive a stake in the ground and say this cannot go on."

The push for national standards comes on the fifth anniversary of the No Child Left Behind (NCLB) Act, the signature education program of President George W. Bush, which requires states to assess what their students have learned. To do so, each state developed its own standards and tests. Proponents say that having national standards is the only way to ensure that the country produces enough scientifically literate graduates to keep the United States competitive in a global economy. But the idea is controversial. The Bush Administration and many legislators and industry leaders say that national standards would undermine state and local authorities, who traditionally are responsible for precollege education. And even proponents of improved math and science education worry that it might divert attention from their goal of improving NCLB, which expires this year.

Learn to earn. Representative Vern Ehlers (*left*) and Senator Chris Dodd say uniform science and math standards will help the U.S. economy.

"The Administration maintains its commitment to local control and supports state development of content standards and assessments," says Chad Colby, a spokesperson for the U.S. Department of Education. Adds Jacque Johnson of the U.S. Chamber of Commerce: "We are not encouraging consideration of national standards because it would become a distraction from moving forward on reauthorizing NCLB this year."

Under the current law, states must test students in reading and math every year in grades 3–8. Schools that fail to make adequate yearly progress on state-designed tests must spend federal funds to improve student performance. Allowing states to establish their own standards and test to those standards, Dodd says, creates a "picture of excellence [that] is an illusion."

Dodd's bill, called the Standards to Provide Educational Achievement for Kids (SPEAK) Act, would provide states with a financial incentive to adopt voluntary national standards developed by the National Assessments Governing Board, which oversees the National Assessment of Educational Progress (NAEP). The legislation creates a $400 million fund that would provide competitive grants to interested states for implementing the core standards and then reward states that do. SPEAK would also extend by up to 4 years the 2014 deadline for every student to reach an acceptable level of learning.

The architects of the legislation argue that it will not only improve the quality of science and math education but also help the country deliver on its promise of equal opportunity. "As a result of varied standards, exams, and proficiency levels, America's highly mobile student-aged population moves through the nation's schools gaining widely varying levels of knowledge, skills, and preparedness," Dodd says. "Voluntary, core American standards [will ensure] that all American students are given the same opportunity to learn to a high standard no matter where they reside."

Proponents of the measure acknowledge that it will face stiff resistance, but they hope to overcome the odds. "We have a window of opportunity now with rising concern about America's performance in math and science and the buzz around national competitiveness," says a congressional aide. "States are realizing that they must improve science and math education in order to attract high-paying jobs."

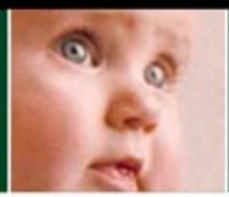
	State assessment	NAEP
4th grade	79%	19%
8th grade	53%	13%

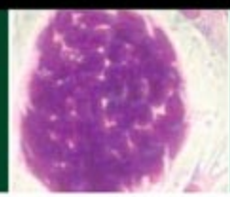
Mixed success. Mississippi students do much better on a state math test than on a national assessment.

Dodd hopes that peer pressure will encourage states to sign up for the voluntary standards, which they will have a role in developing. "I wouldn't want to be the governor who has to explain why his state isn't able to compete with the rest of the country," he quips. And once the standards are ready, he points out, states "will have the option to add additional content requirements, they will have final say in how coursework is sequenced, and, ultimately, states and districts will still be the ones developing the curriculum, choosing the textbooks, and administering the tests. The standards will simply serve as a common core."

–YUDHIJIT BHATTACHARJEE

CREDITS: (TOP) ROGER L. WOLLENBERG/UPI PHOTO/LANDOV; (BOTTOM) SOURCE: NAEP; MISSISSIPPI DEPARTMENT OF EDUCATION; PHOTOS.COM





LETTERS

edited by Etta Kavanagh

Studying Students in Montessori Schools

IN THEIR EDUCATION FORUM "EVALUATING MONTESSORI EDUCATION" (29 SEPT. 2006, P. 1893), A. Lillard and N. Else-Quest present Montessori education as being superior to other types of schools and having "remarkable outcomes." Unfortunately, the analyses backing these value judgments are plagued by methodological and statistical problems and thus do not provide support for such claims.

To evaluate Montessori education, Lillard and Else-Quest measured the performance of children from a single Montessori school—a textbook example of pseudo-replication. The only test performed was thus if this particular school is a good school or not. But not even on that level was the comparison entirely valid, because the pupils in the school were compared with children mainly attending inner-city public schools (72% in 5-year-olds; 78% in 12-year-olds)—the category of schools most often subject to social and economic problems.

Children using a computer at a Montessori school.

Further, the sex ratio in the Montessori sample was equal or skewed toward girls (50% girls in 5-year-olds; 59% girls in 12-year-olds), while the sex ratio in the inner-city public-school sample was skewed toward boys (60% boys in 5-year-olds; 64% boys in 12-year-olds). Girls in these age groups generally outscore boys (*1*, *2*). However, not even with the study set up in this way did the Montessori school come out on top.

Pupils in the girl-dominated Montessori sample rather unsurprisingly scored higher on tests measuring social ability than pupils in the boy-dominated inner-city school sample. But the study also reported that although 5-year-olds in the Montessori sample did better in tests measuring cognitive/academic measures, no such difference could be found in the 12-year-olds.

The only really noteworthy result in this study is that for a sample consisting of mainly girls in a particular school in Milwaukee, several years of Montessori education has resulted in no detectable difference in academic performance in comparison with a group of mainly boys having been subject to schooling in Milwaukee inner-city public schools. Because alternative schools can be assumed to attract more dedicated teachers and often have superior resources to public schools (Montessori schools require a high teacher density and a special set of educational materials) and because young girls tend to outscore young boys academically, this is more a quality statement for Milwaukee public schools than anything else.

To make informed choices about schooling, parents and policy-makers everywhere are in dire need of proper comparisons between different education systems. Unintended misinformation through poorly performed studies only serves to make the current state of confusion over the pros and cons of various education systems worse.

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IN THEIR EDUCATION FORUM "EVALUATING Montessori education" (29 Sept., p. 1893), A. Lillard and N. Else-Quest do not consider that differential peer influences between their test and control groups of students may contribute to the differences they observed. The authors controlled for parental effects by examining only students whose parents had entered a lottery for entry into a Montessori school. However, the students who were unable to attend the Montessori school because their parents "lost" the lottery were dispersed to traditional schools, where they would have been educated with a majority of peers whose parents did not enter the lottery at all. The differences they found in the academic and behavioral performance of students in Montessori and traditional schools may not reflect the superiority of the former educational approach, but the negative effect of peer relationships in the latter.

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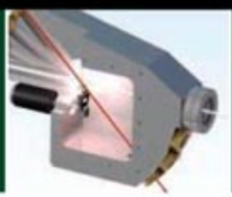
Response

THE MONTESSORI SCHOOL WE STUDIED WAS an inner-city public school [see our note (*3*)] in the same school district as the other 27 city public schools, was given the same per-pupil funding as the district gives all its schools, and received no other funds toward the educational program. Although it is a single school, the traditional Montessori implementation, regulated by the Association Montessori Internationale (AMI), makes it very similar to other AMI Montessori schools; I would be wary of assuming similar results at non-AMI Montessori schools. Still, replication in other school districts is clearly desirable.

Gender did not contribute significantly to any of the differences reported in the paper; in all tests, we found significant differences favoring the Montessori samples, but analyses by gender on these variables at those ages revealed no differences between the boys and girls. In general, gender differences tend to be small enough that they often do not attain significance in studies with small samples. There were gender differences on several tests at age 12, where gender is unbalanced, but in the opposite direction for Montessori



X-ray diffraction of bismuth

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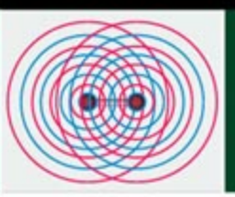

Asymmetry from symmetry

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than the Letter presumes: Montessori boys at age 12 performed best of all the groups on those tests. In addition, the study was not set up to have gender representation differences across samples; the goal was equal representation, but the returned permission slips dictated the distributions.

Although the 12-year-olds had 6 more years of Montessori schooling, and thus one could argue should have shown stronger academic differences than the 5-year-olds, they also had 6 more years of enculturation in their low-income communities and homes that might work against what happens inside the school walls. Although the current environment emphasizes only academic tests, social skills were included in this study, on the grounds that they are extremely important in life—often, one could argue, more important than having superior academic skills.

Contrary to Lindenfors's assumption, traditional Montessori actually has a rather low teacher density. The AMI standard teacher-child ratio is 1:28 to 1:35. Regardless, the notion that teacher-child ratio is related to student achievement is misguided: Relations have sometimes been found in first grade (*1*), but not consistently enough to claim it generally true (*2*).

Also, Montessori is not more expensive than traditional schooling; once a classroom is outfitted with materials (at a cost of roughly $25,000), the costs per year are less (estimated at $800 per year by the North American Montessori Teachers' Association) than in traditional classrooms because there are no textbooks to replace. The notion that per-pupil expenditures have an impact on student achievement is also not upheld by the data (*3*).

MacKinnon makes the excellent suggestion that child outcomes at the Montessori school might be the result of having peers whose parents entered them in a lottery. One way to investigate this is to see whether children in control schools that also admit by lottery (thus, their classmates might have listed that school as their first choice) did better than children at control schools that did not. Milwaukee does not make obvious to an outsider which schools admit by lottery, but they do indicate that Citywide Specialty Schools are more likely to. The control children in our study who were at Citywide Specialty Schools did not as a group perform as well as the children at the Montessori school studied, suggesting that the results were not simply due to schooling with peers whose parents entered them in a lottery.

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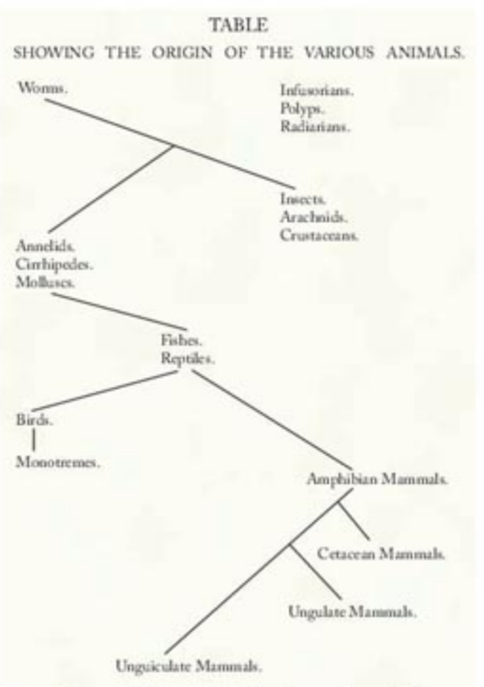
Darwin: Not the First to Sketch a Tree

IN THE PERSPECTIVE BY A. ROKAS, "GENOMICS and the tree of life" (29 Sept., p. 1897), the caption to the accompanying photo identifies Charles Darwin's 1868 notebook sketch as "the first known sketch of an evolutionary tree." This is mistaken. Nearly 60 years earlier, in 1809, Jean Baptiste Lamarck presented an evolutionary tree of the animals in *Philosophie Zoologique* (*1*). Modern evolutionary biologists would benefit from reading Lamarck; there is much nonsense in his work, but there are also quite substantial insights. Lamarck towered over his contemporaries in both the rigor of his evolutionary thought and the identification of a credible, coherent, and falsifiable hypothesis for the mechanism of evolutionary change. That his mechanism was wrong does not take anything away from the originality of his thought (although his failure to test his hypothesis is not consistent with current scientific practice and is largely responsible for his current neglect).



Lamarck's evolutionary tree [redrawn from (*1*)]

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Human Dispersal into Australasia

WE AGREE WITH P. MELLARS THAT LONG-distance dispersal of prehistoric human populations may involve multiple small founder effects with consequent loss of genetic diversity—and possibly also cultural traits—with increasing distance from source ("Going east: new genetic and archaeological perspectives on the modern human colonization of Eurasia," Special Section: Migration and Dispersal, Review, 11 Aug. 2006, p. 796). However, Australian genetic and stone artifact data are not consistent with this pattern.

Genetic studies of the mitochondrial DNA (mtDNA) of indigenous Australians have only just begun, with fewer than 300 individuals sampled from less than 5% of the continent's landmass (*1*–*3*). Even so, observed mtDNA variation in Australians already includes five Australia-specific haplogroups, and more if New Guinea samples are added to represent the landmass that was Sahul for most of the 50,000 to 60,000 years that humans have occupied the island continent (*4*, *5*). Larger, continent-wide samples may well show Australia to have been as genetically diverse as Europe or Africa.

The earliest Australian stone artifact industries consist of small flakes and flake tools with some prepared platform cores and occasional radial or centripetal cores, and are strongly influenced by the form of local stone materials (*6*, *7*). It is unlikely that these industries carry the sort of cultural information that Mellars and others assume. His argument that these are "Mode 4" (Upper Palaeolithic) industries that devolved in response to local conditions (*8*) lacks parsimony, given that

similar assemblages are found in middle Pleistocene and other early contexts in neighboring parts of Southeast Asia (*9*). Also, the balance of evidence indicates only a weak relationship between Mode 4 industries and the spread of modern humans (*8*). In northeast and central Asia, these industries appear to have locally developed (*10*) and subsequently diffused into Europe and the Near East, rather than originating in Africa (*11*, *12*).

Collectively, these data suggest that the cultural and genetic history of Australasia is more complex than a single dispersal model such as "Out-of-Africa 2" allows.

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Response

I APPRECIATE SMITH *ET AL.*'S SUPPORT FOR my general model of a progressive loss in the genetic and technological diversity as modern human populations dispersed from their African homeland to other parts of the world. However, I find the remainder of their arguments unconvincing.

Despite the high genetic diversity of modern Australian and New Guinea populations, the current genetic data indicate unambiguously that all of these populations derive ultimately from the two out-of-Africa mtDNA lineages M and N (in turn derived directly from the African L3 lineage) and from the Y chromosome founder lineages C and F (*1*–*5*). Any subsequent diversity in these populations must derive from genetic mutations that occurred after the original out-of-Africa dispersal around 50,000 to 60,000 years ago [(*1*, *2*, *4*, *5*); my Report].

I am equally unconvinced by their observations on the archaeological data. My own impression is that the earliest Australian technologies are far too simple, generalized, and "expedient" (as they seem to accept) to support any specific technological links with other technologically simple and expedient technologies, such as those from Flores and other earlier Pleistocene sites in southeast Asia (my Report). I am not aware of any convincing Levallois or other "Mode 3" (Middle Palaeolithic) technologies in Australia and see no reason why the Australian technologies should not be viewed as heavily simplified or "devolved" forms of Upper Palaeolithic ("Mode 4") technologies, under the influence of varying raw material effects and other purely local economic adaptations (my Report). I note that they make no reference to the apparent similarities between the forms of the early Australian "horse-hoof" cores and simple forms of single-platform blade cores (my Report). And I am totally unconvinced by the arguments for purely local origins of Upper Palaeolithic/Mode 4 technologies in northeast and Central Asia [my Report; (*6*)]. To employ these data to support some form of multiregional, as opposed to African, origins for modern Australian populations would seem to be poorly founded in either the genetic or archaeological data.

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

CORRECTIONS AND CLARIFICATIONS

Reports: "Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa" by L. J. Abu-Raddad *et al.* (8 Dec. 2006, p. 1603). The first sentence of the paper, "In Africa, an estimated 40 million people are infected with HIV, resulting in an annual mortality of over 3 million (*1*), while over 500 million clinical *Plasmodium falciparum* infections occur every year with more than a million malaria-associated deaths…" is incorrect. These numbers refer to worldwide numbers for both infections, not just in Africa. The number of HIV-infected persons in Africa is approximately 25 million, and the number of malaria infections is roughly 350 million.

Perspectives: "How fast does gold trickle out of volcanoes?" by C. A. Heinrich (13 Oct. 2006, p. 263). In line 7 of the first full paragraph of column 3, "10 to 20 mg" should be "10 to 20 μg."

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Rapid Advance of Spring Arrival Dates in Long-Distance Migratory Birds"

Christiaan Both

Jonzén *et al.* (Reports, 30 June 2006, p. 1959) proposed that the rapid advance of spring migration dates of long-distance migrants throughout Europe reflects an evolutionary response to climate change. However, most migrants should not advance their migration time because the phenology of their breeding grounds has not changed. It is more likely that migration speed has changed in response to improved environmental circumstances.

Full text at www.sciencemag.org/cgi/content/full/315/5812/598b

RESPONSE TO COMMENT ON "Rapid Advance of Spring Arrival Dates in Long-Distance Migratory Birds"

Niclas Jonzén, Andreas Lindén, Torbjørn Ergon, Endre Knudsen, Jon Olav Vik, Diego Rubolini, Dario Piacentini, Christian Brinch, Fernando Spina, Lennart Karlsson, Martin Stervander, Arne Andersson, Jonas Waldenström, Aleksi Lehikoinen, Erik Edvardsen, Rune Solvang, Nils Chr. Stenseth

Both's comment questions our suggestion that the advanced spring arrival time of long-distance migratory birds in Scandinavia and the Mediterranean may reflect a climate-driven evolutionary change. We present additional arguments to support our hypothesis but underscore the importance of additional studies involving direct tests of evolutionary change.

Full text at www.sciencemag.org/cgi/content/full/315/5812/598c

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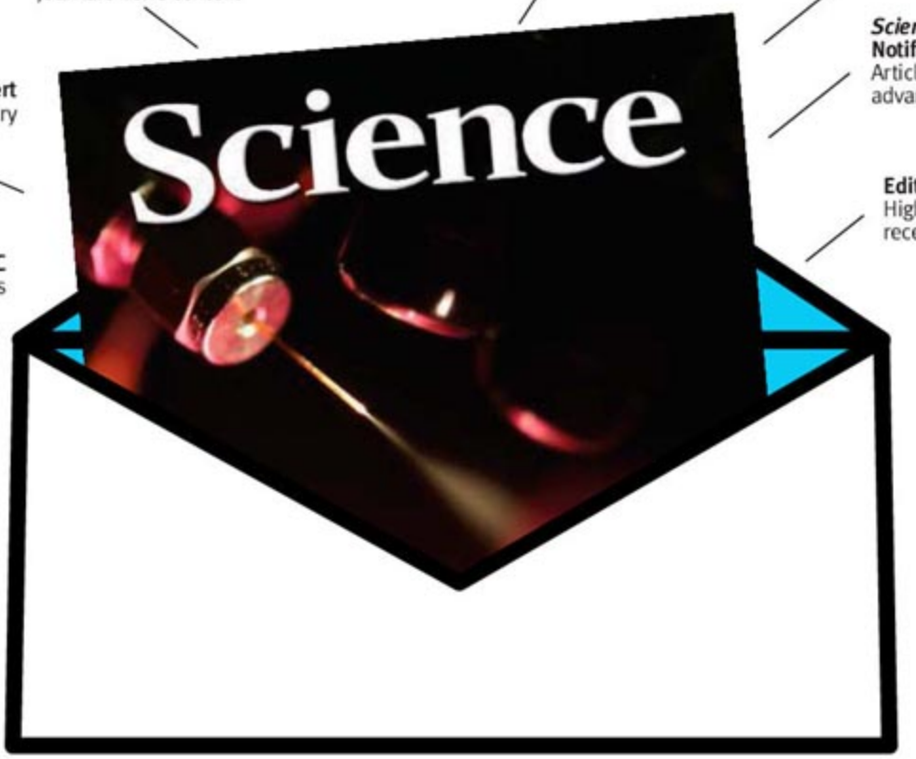

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Highlights of the recent literature

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MEDICINE

Developing a Different Perspective on Disease

Linda Adair

For many decades, efforts to prevent chronic disease focused on modifying aspects of adult life-style that contribute to nutritional excesses—too much energy intake relative to too little energy expenditure. Paradoxically, a rapidly growing body of evidence from animal experiments and human epidemiologic research suggests that chronic diseases have early life origins related to inadequate nutrition. These findings emphasize the need for a life course perspective on disease, with prevention beginning prior to conception.

Over the past two decades, a new field of research into adult health and disease has emerged that focuses on early life and developmental origins. The basic premise of such inquiry is that very early events in life—in particular, exposure to environments characterized by nutritional insufficiency—induce structural and metabolic changes that enhance survival in resource-poor conditions. When, however, previously undernourished individuals subsequently experience nutritional sufficiency or excess, their adaptive characteristics become a liability and increase their risks of acquiring numerous chronic diseases.

The growth of research on early origins of adult disease was stimulated in the late 1990s by David Barker's observations that coronary heart disease death rates in Hertfordshire, United Kingdom, were inversely related to birth weight. This work was followed by a large number of papers showing inverse associations of birth weight (which was taken as a measure of the quality of the fetal environment) with other adult disease outcomes and by experimental studies in animals to identify the mechanisms through which prenatal nutrition might influence adult hypertension, diabetes, and other chronic diseases. Although the animal evidence was compelling, the idea of "fetal programming" in humans was initially met with skepticism. Today, owing to the accumulation of a large body of experimental and epidemiologic evidence from around the world, the idea has gained wider acceptance. Moreover, the field has broadened well beyond its initial focus on birth weight and the fetal environment to consider the entire developmental sequence from conception to adulthood as a means to understand disease etiology. The World Health Organization (WHO), recognizing the importance of early environments, now advocates the adoption of a life course perspective on chronic disease (*1*).

Developmental Origins of Health and Disease

Peter Gluckman and Mark Hanson, Eds.

Cambridge University Press, Cambridge, 2006. 541 pp. $150, £90. ISBN 9780521847438.

Arriving at a period of peak growth in the field, Peter Gluckman and Mark Hanson's *Developmental Origins of Health and Disease* makes a timely and important contribution. The edited volume offers an excellent integration of theory, evidence, and implications. Nicely encompassing the range of research in the field, it compiles work by more than 70 experts, primarily from Europe, Australia, and New Zealand. Gluckman (an endocrinologist and perinatal biologist at the Liggins Institute, University of Auckland) and Hanson (at the University of Southampton Medical School) are eminently qualified to compile this synthesis of the field.

A life course perspective.

In addition to an introductory overview, the editors provide a conceptual basis for the developmental origins approach that is strongly grounded in evolutionary theory. They argue that organisms are capable of "predictive adaptive responses": the ability to use information about the current environment to develop strategies to enhance not only immediate survival but also long-term survival under similar conditions in the future. According to their perspective, when there is a mismatch between the early and later environment—as happens when previously malnourished individuals encounter fast food and spend too many sedentary hours in front of the television—formerly successful strategies may be ill suited to the new challenges and thus lead to pathologies. The contributors carry this theme through subsequent chapters.

The book's central portion offers in-depth coverage of the evidence for the developmental origins hypothesis and the proposed underlying mechanisms. The book avoids the unappealing "one disease per chapter" format and instead presents an integrated, systems-oriented view of the physiology and mechanisms. Collectively, the contributors explain how things work, what can go wrong, and why it matters. They cover diverse topics including early influences on gene expression, the role of mitochondria, and the effects of various hormone systems. Some chapters integrate information from the experimental animal and human epidemiologic literatures, whereas others focus primarily on human studies. The cardiovascular and related systems, which are the best studied in the context of developmental origins, receive extensive coverage. The authors also apply the approach to chronic diseases such as those that affect the musculoskeletal and respiratory systems, the brain, and aging.

The developmental origins perspective emphasizes the ongoing interaction of the organism with stressors in the environment across the entire life cycle. Nutritional insufficiency is thought to have the greatest import, and it is well covered. The volume also does an admirable job of considering other stressors with long-term effects, including hypoxia and exposure to environmental toxins.

The book's last section explores the implications of the developmental origins approach for primary prevention, public health, and, in particular, health in developing countries. People are most likely to encounter a mismatch between early and later environments in settings characterized by the transition from marginal nutrition to chronic positive energy balance. For example, because of changes in food production and mechanization, older children and adults born when fetal and infant growth restriction were common are now consuming more calories and expending less

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energy in work and leisure time physical activity, which contributes to the rise of obesity as a worldwide public health problem. The potential implications of this mismatch can be best appreciated by considering global trends in chronic diseases. According to WHO projections, cardiovascular disease is emerging as the top cause of mortality in developing countries and by 2020 will account for one-third of all deaths. More than 228 million will suffer from diabetes, with India having more diabetics than any other country. By emphasizing the role of developmental processes and the nutritional history of populations, the developmental origins perspective promises valuable insights into the causes and consequences of these new health challenges. It will complement the conventional focus on the roles of genetic susceptibility and modifiable adult behaviors.

Researchers will find *Developmental Origins of Health and Disease* to be a well-referenced resource that documents the state of the art in the field and serves as a source of new ideas. Students of human and developmental biology and health practitioners should also keep the volume in close reach. It challenges readers to consider new paradigms for disease prevention that recognize epigenetic influences as well as genetics and take into account the complex interplay among genes, environment, and developmental history. The volume inspired me to think differently and to develop a new set of research questions to answer with my cohort data from a developing country, and I hope that others will be similarly affected.

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10.1126/science.1134320

ANTHROPOLOGY

Otherness—When Killing Is Easy

The Altruism Equation
Seven Scientists Search for the Origins of Goodness
by Lee Alan Dugatkin
Princeton University Press, Princeton, NJ, 2006. 202 pp. $24.95, £15.95. ISBN 9780691125909.

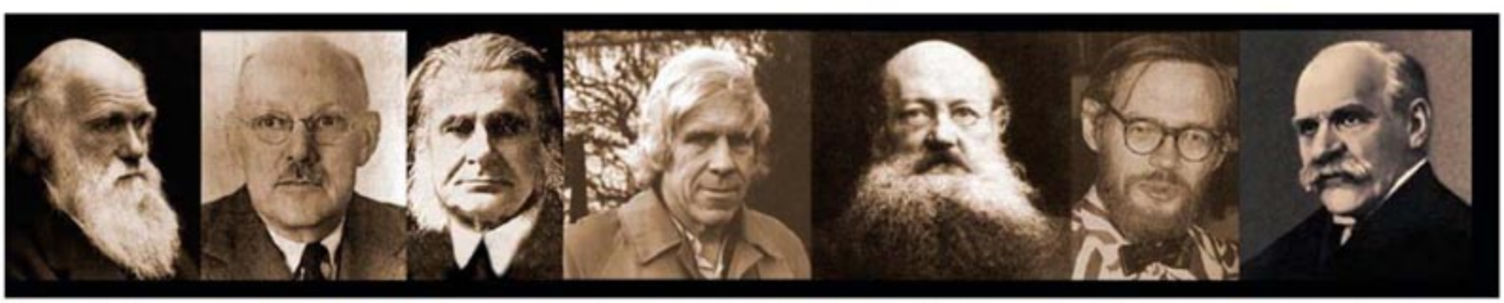
Conflict
Martin Jones and A. C. Fabian, Eds.
Cambridge University Press, Cambridge, 2006. 184 pp. $40, £25. ISBN 9780521839600. Darwin College Lectures.

Natural selection underpins the evolution of good and evil in human beings. This claim may sound far-fetched, but increasingly archaeological and anthropological evidence and the work of a small coterie of theoreticians indicate that Paleolithic people clustered together using common languages and culture to develop norms that protected equality, liberty, and fraternity and thus forged cooperative groups that behaved altruistically. Such bonds allowed the group to present a united front to less-fortunate neighbors, thereby providing backup for dispatching rivals in combat with little risk to self and probably with considerable benefit in terms of resources grabbed. These themes are explored in contrasting approaches in two exhilarating books: *The Altruism Equation* explores altruism through the eyes of half a dozen thinkers of the past two centuries, and *Conflict* offers essays on our embattled species collected from eight living scholars.

According to Lee Alan Dugatkin (a behavioral ecologist at the University of Louisville), the grail is $r \times b > c$, Hamilton's rule for altruism by kin selection. This equation states that altruism can occur between individuals if their genetic relatedness (r), multiplied by the value of the benefit (b) bestowed by an altruistic act, exceeds the cost (c) of undertaking that action; the larger r is, the more likely altruism will evolve. Among the mass of evidence that substantiates a genetic basis for altruism, deep in the book we find that for the plains spadefoot toad (*Spea bombifrons*) relatedness is literally a matter of taste: carnivorous morphs spit out their nearest and dearest but eat those least related.

The Altruism Equation is an engaging book with devoted enthusiasm for the ideas of the main protagonist, William Hamilton. On the way there are irritations, not least the author unfairly bemoaning the lack of insight into economic modeling by all of Hamilton's predecessors, including Charles Darwin, Thomas Huxley, and Warder Clyde Allee. He also tours through the mathematical lapses of Ronald Fisher, J. B. S. Haldane, and Sewall Wright, similarly wondering why they were not so able. Despite all this mischief, Dugatkin's enthusiasm rises well beyond the irritations, and his account offers much to think about.

Through his portrayal of George Price, Dugatkin raises an important link in considering the evolution of altruism and conflict. Price, a close friend of Hamilton, turned Hamilton's rule on its head and developed an explanation for the evolution of spite (which occurs when individuals in groups are on average less closely related than individuals within the population) by using a new mathematical tool, covariance. He found that even if a spiteful act diminished the fitness of the perpetrator, it would decrease the fitness of the victim (and rival) even more. Price, an occasional reporter for *Science*, went on to elaborate the use of game theory in behavioral sciences while living in squalor, constantly giving his belongings away. He underwent a personal paradigm shift from atheism to profound religious belief, adopted extreme altruism, and died in poverty by his own hand.



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Pioneers in the search for the origins of goodness. Left to right: Charles Darwin, Warder Clyde Allee, Thomas Henry Huxley, William Hamilton, Petr Kropotkin, George Price, and John Burdon Sanderson Haldane.

None of the essays in the volume edited by Martin Jones (Department of Archaeology, University of Cambridge) and Andrew Fabian (Institute of Astronomy, University of Cambridge) can dispel the conclusion that conflict lies at the heart of human behavior. It seems depressing that natural selection has taken us this way and that, although we don't need much relatedness to each other to prompt us to behave well, slight difference provokes rivalry that can end in a fight to the death.

Richard Wrangham's contribution explores the parallels of the lethal desire to pick off unrelated male rivals in our nearest relatives, chimpanzees (*Pan troglodytes*). Like human beings, chimps often kill one another—usually by a gang beating up a solitary male foraging near a territorial boundary. In contrast, battles between groups are not usually to the death; they are mostly show and bravado. By murdering individuals, the potential of harm in future battles is reduced because of the attrition of males from the neighboring group. But the gains don't end with damage limitation: the ideal is to eliminate all the males in the rival group. The former group's foraging territory and females will then benefit the prevailing group. Wrangham makes an interesting contrast with bonobos (*Pan paniscus*), who apparently live peacefully together because of ecological differences that allow them to forage in continuous close contact, thus avoiding being picked off by their rivals.

Among human beings, it is no surprise that lethal conflict predominates among men. Simon Baron-Cohen discusses sex differences in the brain and what he recognizes as the extreme male mind. He hypothesizes that men tend to fact-based systemizing whereas the female mind tends to make intuitive leaps and to have well-developed social and linguistic abilities. Somewhat frustratingly for the theme of the book, he doesn't elaborate much on how this extreme mind fits men for conflict nor on the roots of male-female conflict. Later in the volume, the paradox of seeing women in combat is one of the themes explored by Kate Adie, a former BBC war correspondent. But she concentrates on describing the difficulties of observing and reporting on war, because these handicaps must be overcome if media coverage is to increase our understanding of conflict and its consequences.

Several other essays in the Darwin College Lectures volume bridge many of the anthropological consequences of the natural selection of conflict: for example, Barry Cunliffe considers the evolution of state-sponsored war over the centuries and David Haig discusses the torment of decision-making. Of particular currency is a fascinating account of the conflict in the Middle East. Lisa Anderson points out that despite the antiquity of conflict in the region, casualties have actually been small compared with many other war zones. Why do we get so anxious about it? Perhaps, she contends, because the general region is the nexus of several modern civilizations and persistent conflict there is perceived to be particularly undermining and threatening. Exploring the influence of national boundaries, elective identities, and single and divided loyalties, Anderson concludes that the turmoil in the region arises within "societies and traditions that are struggling to define meaning and membership."

Despite the stark conclusions emerging from both books, an enduring belief in a benign future for humankind paradoxically prompts most of the subjects and the contributors to end on an optimistic note.

–CAROLINE ASH

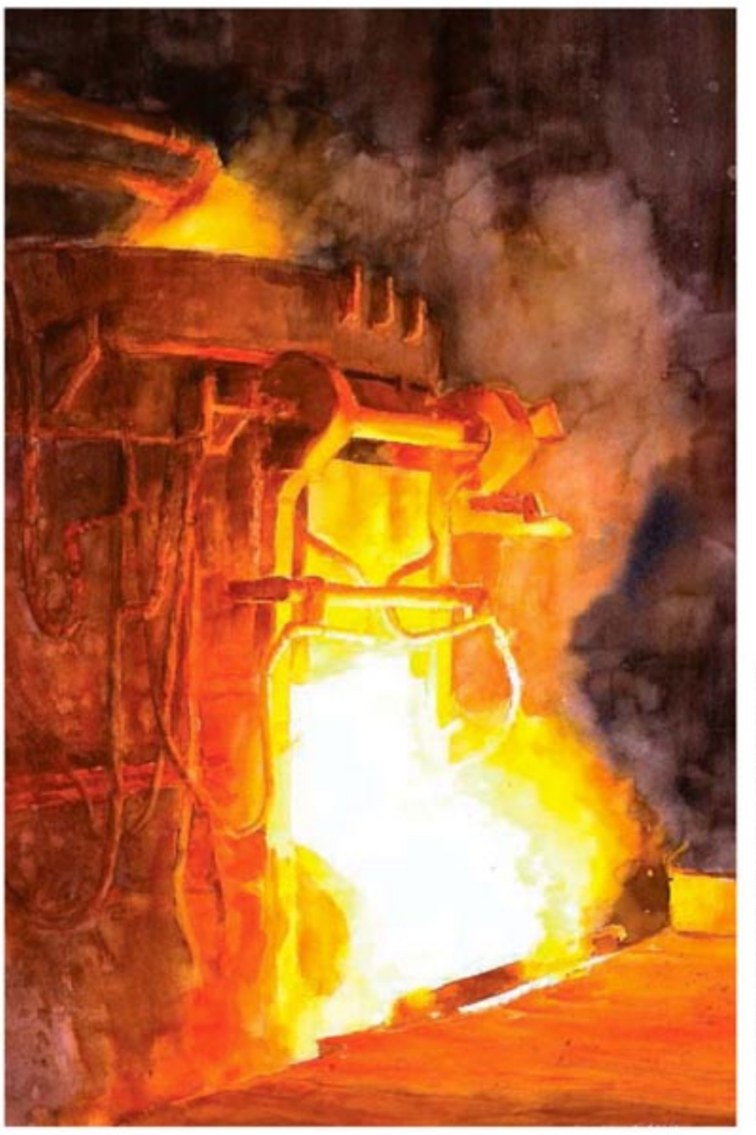
10.1126/science.1138815

BROWSING

Born of Fire: The Valley of Work.

Industrial Scenes of Southwestern Pennsylvania. Barbara L. Jones, with Edward K. Muller and Joel A. Tarr. Westmoreland Museum of American Art, Greensburg, PA, 2006. 160 pp. $37.50. ISBN 9780822943259.

By the early 1900s, the Pittsburgh region was the steel-making capital of the world. Its valleys were lined with iron foundries, steel mills, coke works, and rail yards; its rivers crowded with barges and bridges; its skies marked with billowing smokes by day and "pillars of fire" by night. Resident and visiting artists were struck by the drama and beauty of the industrial facilities and landscapes, which they portrayed in oils, watercolors (right, Cynthia Cooley's *Furnace Door*, 1999), drawings, and photographs. They also recorded the laborers' arduous living conditions and industry's devastating impact on the environment. In this catalog, prepared for a 2006 exhibit of the Westmoreland Museum's Scenes of Industry collection, Jones discusses the images and the artists who created them. Muller and Tarr offer an informative sketch of the rise and decline of southwestern Pennsylvania's coal and steel industries. Sixty works from the collection are on display at the Rhineland Industrial Museum in Oberhausen, Germany, 4 February to 1 May 2007, and will travel through 2010.



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ETHICS

The ISSCR Guidelines for Human Embryonic Stem Cell Research

The International Society for Stem Cell Research describes major principles that should guide ethical stem cell research.

George Q. Daley,[1*] Lars Ahrlund-Richter,[2] Jonathan M. Auerbach,[3] Nissim Benvenisty,[4] R. Alta Charo,[5] Grace Chen,[6] Hong-kui Deng,[7] Lawrence S. Goldstein,[8] Kathy L. Hudson,[9] Insoo Hyun,[10] Sung Chull Junn,[11] Jane Love,[12] Eng Hin Lee,[13] Anne McLaren,[14] Christine L. Mummery,[15] Norio Nakatsuji,[16] Catherine Racowsky,[17] Heather Rooke,[1,18] Janet Rossant,[19] Hans R. Schöler,[20] Jan Helge Solbakk,[21] Patrick Taylor,[1] Alan O. Trounson,[22] Irving L. Weissman,[23] Ian Wilmut,[24] John Yu,[25] Laurie Zoloth[26]

Human embryonic stem (ES) cells are valuable for biomedicine, but differing cultural, political, legal, and religious perspectives are potential barriers to international collaboration in this fledgling field. Recognizing the need for scientists to act transparently, to serve the public interest, and to preserve public trust, the International Society for Stem Cell Research (ISSCR) convened a task force to formulate guidelines for human ES cell research. The ISSCR guidelines were written by scientists, ethicists, and legal experts from 14 countries (*1*).

The ISSCR guidelines encompass the core values put forth by the Committee on Guidelines for Human ES Cell Research of the U.S. National Academy of Sciences (U.S. NAS) (*2*) and the Regulations of the California Institute for Regenerative Medicine (*3*), and acknowledge thoughtful governmental regulations already in place in several countries, particularly that of the Human Fertilisation and Embryology Authority of the United Kingdom (*4*). The ISSCR is the principal scientific society for stem cell scientists and transcends institutional, regional, and national political boundaries.

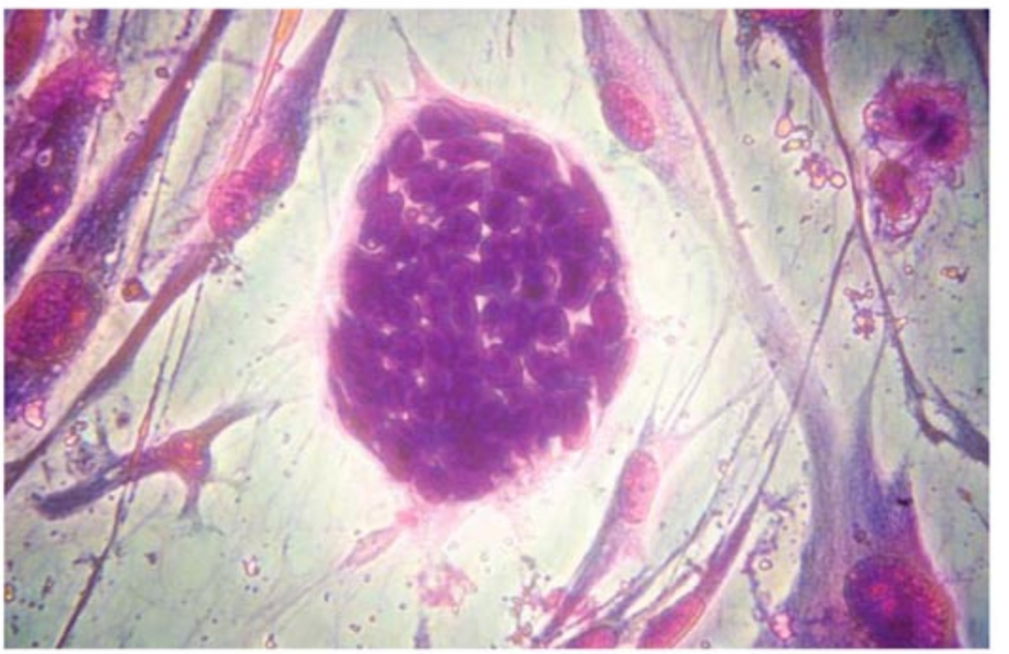
The ISSCR guidelines focus on research pertinent to derivation and use of pluripotent human stem cell lines and are not meant to encompass somatic (adult) stem cell research or human embryo or fetal tissue research. The ISSCR guidelines aim to facilitate international collaboration by encouraging investigators and institutions to adhere to a uniform set of practices. The ISSCR guidelines are subservient to all applicable laws and regulations of the country or region where the actual research takes place.

Major Principles

Call for oversight. Biomedical research is already subject to regulation and oversight. However, because human ES cell research raises unique and sensitive issues and requires specialized expertise to judge both scientific merit and ethical propriety, the ISSCR guidelines call for a specialized oversight process to complement existing institutional review boards. In contrast to the U.S. NAS guidelines, which stipulated that institutions engaged in human ES cell research should form an ES cell research oversight (ESCRO) committee, the ISSCR guidelines do not specify the precise form of stem cell research oversight (SCRO). The ISSCR guidelines specify the key elements of a single rigorous review at the institutional, regional, national, or international level, thereby eliminating redundancy and allowing flexibility for varied oversight mechanisms in different countries.

Permissible and impermissible research. The ISSCR guidelines prohibit (i) all experiments that lack a compelling scientific rationale or raise strong shared ethical concerns—in particular human reproductive cloning; (ii) in vitro culture of human embryos beyond 14 days or the formation of the primitive embryonic streak; and (iii) the interbreeding of animals likely to harbor human gametes.

The "14-day limit," first articulated in 1984 by the Warnock committee of the U. K. Human Fertilisation and Embryology Authority (*5*), is widely accepted by researchers in the human stem cell and fertility fields. It recognizes the significant biological distinctions between the earliest human embryos,



COURTESY OF M. WILLIAM LENSCH, CHILDREN'S HOSPITAL BOSTON

How can ethical principles for research encompass cultural differences? Shown is a human embryonic stem cell colony, on a background of mouse embryonic fibroblast feeder cells, stained with Wright-Giemsa to highlight the individual cells of the colony.

[1]Children's Hospital Boston. [2]Karolinska Institutet. [3]GlobalStem, Inc. [4]The Hebrew University. [5]University of Wisconsin Law School. [6]Bird & Bird, Beijing, China. [7]Peking University. [8]Howard Hughes Medical Institute, University of California, San Diego School of Medicine. [9]Berman Bioethics Institute, Johns Hopkins University. [10]Case Western Reserve University School of Medicine. [11]Institute of Global Management, Seoul, Korea. [12]Wilmer Cutler Pickering Hale and Dorr LLP. [13]National University of Singapore. [14]Cambridge University. [15] University of Utrecht Medical School. [16]Kyoto University. [17]Brigham and Women's Hospital, Harvard Medical School. [18]International Society for Stem Cell Research. [19]University of Toronto. [20]Max Planck Institute for Molecular Biomedicine. [21]University of Oslo and University of Bergen. [22]Monash University. [23]Stanford University School of Medicine. [24]University of Edinburgh. [25]Genomics Research Center, Academia Sinica, Taiwan. [26]Feinberg School of Medicine, Northwestern University. [For complete addresses, see SOM.]

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which have not yet established even the most rudimentary rostral and caudal orientation (the primitive streak), and an embryo that has begun to initiate organogenesis. The U.S. NAS guidelines prohibit the mixing of cells of any nature with the pre-streak embryo. This restriction excludes a number of experiments considered standard in animal embryology, including cell aggregation studies to investigate the segregation of primitive embryonic blastomeres into inner cell mass and trophectoderm. Such experiments might yield insights into the origins of stem cells and might enhance the efficiency of ES cell derivation. The ISSCR Task Force reasoned that experiments with sound scientific rationale that respect the 14-day limit are permissible if they pass a thorough SCRO review.

The ISSCR guidelines diverge subtly from the U.S. NAS guidelines in restrictions placed on breeding of animals that might carry human gametes. Such experiments might be justified to investigate the consequences of tissue repair or regeneration on reproductive behavior or function, and they could be done with safeguards to prevent any inadvertent fertilization events (e.g., sterilization). The ISSCR guidelines place the onus on the SCRO process to evaluate permissibility of any particular experiment.

Experiments that are permissible only after SCRO review and approval include derivation of new lines or creation of animal chimeras, especially experiments likely to result in extensive chimerism of the brain or germ line. The ISSCR guidelines provide a means for excluding in vitro experiments with existing human ES cell lines from review, as appropriate, and exclude from SCRO review routine procedures that raise no appreciable moral concerns, such as assays of teratoma formation from human ES cell lines. Under the U.S. NAS guidelines, the teratoma assay requires ESCRO committee review because it entails the creation of a chimeric animal. We anticipate that other procedures may become exempt from SCRO review as the field evolves.

Requirement for explicit consent. For use of somatic cell nuclei in nuclear transfer experiments, the ISSCR guidelines call for obtaining contemporaneous and explicit consent from all somatic cell donors. Such a rigid requirement reinforces a position stated by the U.S. NAS guidelines to protect individuals who might not want their tissues unwittingly used in human ES cell research. For the research use of embryos generated with donated gametes, the ISSCR guidelines reaffirm the need for explicit consent from both gamete donors. In the future, informed consent for all gamete donors should include the possible use of donated materials and their derivatives in human stem cell research.

Financial considerations. In some nations, like the United States, women who provide their eggs to infertile couples are routinely compensated—that is, provided money in addition to reimbursement of direct expenses—in a range that varies widely but is typically from $2500 to $5000 (*6*). Some believe that high payments may unduly induce women to ignore the risks of hormonal stimulation and surgical egg retrieval and thus may undermine the voluntary nature of women's choices to provide their eggs to infertile couples. Task force members had varied opinions on what financial accommodations should be allowed for donation of oocytes for research purposes. Some felt that altruism should be the only permissible motivation for research donation; others felt that asking women to bear the significant burden of time, effort, discomfort, and risk of donation without compensation was itself unfair and exploitative.

There was consensus for providing reimbursement of direct expenses incurred during the process of providing oocytes, although there was concern that even this financial consideration might invite abuse. The Task Force noted that healthy research volunteers who undergo invasive research procedures like bone marrow biopsy or colonoscopy are sometimes compensated, but could not reach consensus on the permissibility of even a modest honorarium for providing oocytes. The Task Force concluded that research and ethical review committees are experienced in evaluating financial considerations and that substantial literature documents their ability to distinguish undue inducements from payments that appropriately acknowledge the interests of the subject (*7*–*10*). Thus, the Task Force agreed to allow the SCRO process to determine the financial considerations involved in egg procurement, guided by the principle that "there must be a detailed and rigorous review to ensure that reimbursement of direct expenses or financial considerations of any kind do not constitute an undue inducement."

Encouraging compliance. To encourage adoption of the ISSCR guidelines by the research community, and as a mechanism of enforcement, the guidelines call for journal editors and granting agencies, as a stipulation for publication or funding, to require investigators to attest to compliance with the ISSCR guidelines or an equivalent set of regulations. To set the guidelines into practice, sample informed-consent documents for the procurement of human research materials were created and subjected to extensive peer review by an external international group of ethicists, research policy experts, and leaders of institutional review boards and ES cell research oversight committees. These documents encompass the principles articulated in the ISSCR guidelines and are available from the ISSCR Web site (*11*). The ISSCR hopes to establish a database of human ES cell lines that have been derived in accordance with the ISSCR guidelines.

Finally, the ISSCR guidelines state that researchers engaging in human ES cell research must make their materials readily accessible to the biomedical research community. The guidelines thus include recommendations for the derivation, banking, storage, and distribution of research materials, and provide a sample Material Transfer Agreement to facilitate exchange of research materials (*11*).

The Future

The ISSCR leadership is committed to ongoing review and revision of the guidelines, and appreciates that new research in science, ethics, law, and policy will challenge us with new questions. We are hopeful that the many communities affected by and attentive to stem cell research will consider these guidelines a call for their robust participation in the processes that decide the direction of research. The ISSCR seeks the support of its membership, members of other scientific societies, our institutions, and the public to promote adoption of the ISSCR guidelines globally.

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12. See SOM for conflict-of-interest statements.

Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/603/DC1

10.1126/science.1139337

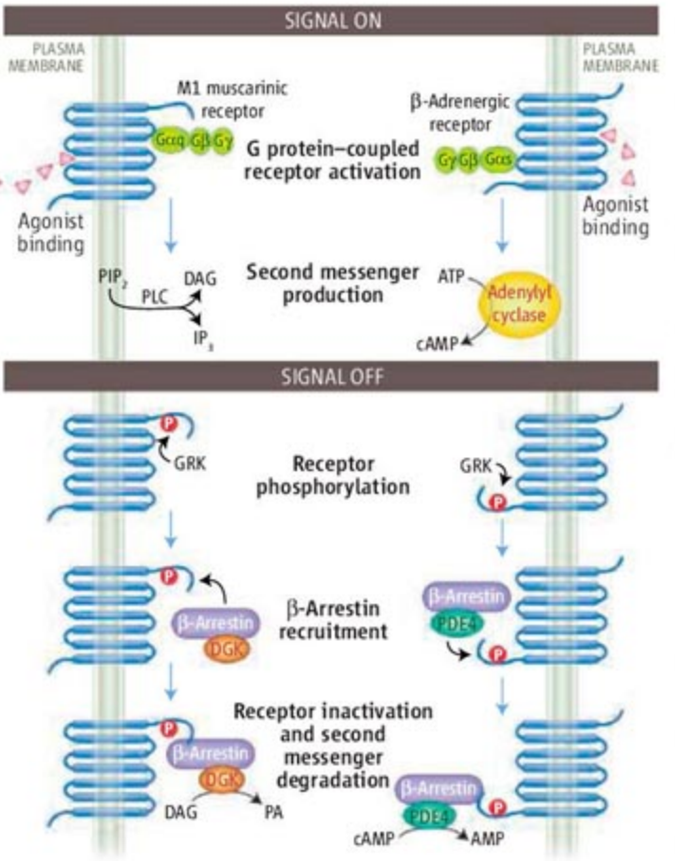
CELL SIGNALING

β-Arrestin, a Two-fisted Terminator

β-arrestin escorts enzymes to activated receptors, catalyzing the demise of signals that are generated. This may be a common theme among G protein–coupled receptors.

Eileen F. Grady

Once a cell detects a signal—say, a hormone or a factor that simulates growth—it must relay that information to its interior so that it can respond appropriately. This scenario often involves a receptor at the cell's surface, poised to transmit the signal through a circuit of intracellular molecules. Just as important as its activation, a signaling pathway also needs to be shut down, or the cell risks an undesirable response—perhaps uncontrolled proliferation or even cell death. The molecule β-arrestin has long been known to block continued receptor signaling by associating with activated receptors, a phenomenon demonstrated most fully with G protein–coupled receptors (*1*, *2*). β-Arrestin also acts as a scaffold, upon which other signaling molecules assemble to participate in downstream signaling events (*3*). On page 663 of this issue, Nelson *et al.* (*4*) expand the capabilities of β-arrestin. It not only directly terminates receptor activation, it also simultaneously facilitates the degradation of the immediate signaling molecule produced by an activated receptor. These findings are exciting because β-arrestin has this dual effect for a completely different receptor and intracellular signaling molecule (*5*). Therefore, these coordinated functions of β-arrestin may be a common theme among G protein–coupled receptors, the largest family of cell surface signaling receptors.



Signal arrest. The activation of two different G protein–coupled receptors by agonists generates second messenger signaling molecules. The receptors are desensitized by phosphorylation by G protein–coupled receptor kinase (GRK) and subsequent binding of β-arrestin. β-Arrestin also simultaneously recruits different enzymes [diacylglycerol kinase (DGK); phosphodiesterase 4 (PDE4)] to degrade second messengers, further terminating signaling. Phosphatidic acid (PA) can act as another second messenger.

In the case of the M1 muscarinic receptor, the G protein–coupled receptor examined by Nelson *et al.*, β-arrestin recruits diacylglycerol kinase from the cytosol to the activated receptor. The enzyme degrades diacylglycerol, the signaling molecule or "second messenger," that is generated in response to M1 muscarinic receptor activation (see the figure). Through degradation of diacylglycerol, β-arrestin negatively regulates protein kinases C and D. In a twist to this signaling shutdown, β-arrestin simultaneously initiates other signaling events, because diacylglycerol degradation generates phosphatidic acid, a second messenger involved in events such as vesicle trafficking and kinase activation.

Nelson *et al.* show that under basal conditions, any of seven diacylglycerol kinases (α, β, γ, δ, ε, ζ, and ι) can directly associate with β-arrestin (type 1 or 2) when the molecules are overexpressed in cultured mammalian cells. The ability of all of these diacylglycerol kinases to interact with β-arrestin increases the likelihood of a general mechanism for regulating the M1 muscarinic receptor signaling pathway. The authors detected diacylglycerol kinase ζ in a complex with endogenous β-arrestin; moreover, diacylglycerol kinase activity was associated with endogenous β-arrestin. Surprisingly, stimulation of endogenous M1 muscarinic receptors with carbachol, or stimulation of protein kinase C with phorbol ester, did not increase the association of diacylglycerol kinase ζ with β-arrestin. This suggests that interaction between the two proteins is maximal under basal conditions, and therefore constitutive. If so, the availability of diacylglycerol kinases may depend on the available cytosolic β-arrestin pool. And if this is the case, activation of heterologous receptors may alter the ability of a cell to degrade a signal generated by a second receptor.

Perry *et al.* (*5*) showed that β-arrestin causes degradation of a second messenger (cAMP) generated by activated β_2-adrenergic receptors by recruiting phosphodiesterase 4 isoforms to the activated receptor (see the figure). Therefore, a common theme among G protein–coupled receptors might be that β-arrestin both desensitizes a receptor by preventing it from further activating a heterotrimeric G protein (this consequently decreases second messenger production), and degrades second messenger molecules by recruiting appropriate enzymes (see the figure). The phosphodiesterase, diacylglycerol kinase, and the receptors by which they affect signaling have very disparate structures, making this dual role of β-arrestin, and its ability to regulate dissimilar receptors, even more remarkable.

How can β-arrestin interact with all these proteins? A structural analysis of the binding sites of β-arrestin is long overdue; however, some information has been gleaned from studies on clathrin (*6*, *7*). Clathrin binds β-arrestin with high affinity only when β-arrestin is dephosphorylated, a modification that occurs upon binding to the receptor. The receptor–β-arrestin interaction induces a conformational change in β-arrestin that exposes a C-terminal binding site for clathrin (*2*, *8*). Association with clathrin triggers endocytosis of the receptor, another means by which β-arrestin can shut down signaling.

Perhaps phosphorylation of cytosolic β-arrestin enables interaction with other nonreceptor partners such as diacylglycerol kinase. Nelson *et al.* used deletion and truncation

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mutants to determine that β-arrestin binds to a highly conserved cysteine-rich domain present in all diacylglycerol kinases, thus accounting for its interaction with all the enzyme isoforms. The authors also determined that diacylglycerol kinase ζ binds to a site in the C terminus of β-arrestin that is different from the one that binds to clathrin. What about other proteins that bind β-arrestin, including the small GTP-binding protein Rho and components of the MAP kinase signaling cascade, among others (*2*)? Only some of these binding sites have been mapped, and most appear distinct. Are arrestin dimers also required to enable receptor signaling regulation?

Nelson *et al.* also found that carbachol-stimulated phosphatidic acid production increased when β-arrestin was overexpressed in cells, whereas production decreased in cells depleted of β-arrestin—so low that a major role for β-arrestin in regulating phosphatidic acid production due to receptor activation is indisputable. In a related report, diacylglycerol kinase was isolated and localized with phosphatidylinositol 4-phosphate 5-kinase, an enzyme that is activated by phosphatidic acid and generates phosphatidylinositol 4,5-bisphosphate. Phosphatidylinositol 4,5-bisphosphate is the precursor for the second messenger diacylglycerol (*9*). It is unknown whether β-arrestin regulates the activity of phosphatidylinositol 4-phosphate 5-kinase directly or only through formation of phosphatidic acid.

The binding of β-arrestin to diacylglycerol kinases versus G protein–coupled receptors was discriminated by using a form of β-arrestin 2 lacking the N terminus, a region that his required for interaction with receptors.owever, this form could still bind to diacylglycerol kinases and acted as a dominant negative β-arrestin, causing retention of diacylglycerol kinase ζ in the cytosol. It also blocked phosphatidic acid production by the diacylglycerol kinase–β-arrestin pathway (rather than by phospholipase D). Because diacylglycerol is a second messenger for many diverse receptors, as well as a regulator of transient receptor potential channel activity, this role of β-arrestin may have widespread physiological consequences (*10*).

The findings by Nelson *et al.* are provocative because of the questions they raise: How much β-arrestin is required for a cell to regulate signaling normally? Is this different for distinct cells with discrete metabolic activity or modes of signaling? It is assumed that β-arrestin is present in all animal tissues and cells, but studies of β-arrestin localization are few. What other receptors types (*11*, *12*) are regulated in a similar manner? If β-arrestin similarly regulates signaling for other receptors, what other enzymes are recruited by β-arrestin? A whole new group of enzymes participating in signal termination may become the newest nonreceptor partner for β-arrestins (*2*, *7*).

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ECOLOGY

Tackling Ecological Complexity in Climate Impact Research

Longer time scales and evaluation of temporal effects are essential for analysis of ecosystem perturbations.

Gian-Reto Walther

Evidence for the ecological impact of global climate warming has become increasingly compelling. For example, plants and animals adapt the timing of their life cycles or shift their ranges toward higher latitudes and/or altitudes in response to warmer climatic conditions (*1*). However, as the study by Suttle *et al.* (*2*) on page 640 of this issue shows, the observed responses of individual plant and animal species are just the starting point of a cascade of interweaved responses and feedback processes. In their field experiment, Suttle *et al.* imposed different projected precipitation regimes over grassland in California to evaluate the effects of these treatments on plant productivity and species composition of plants, invertebrate herbivores, and their natural enemies (*2*).

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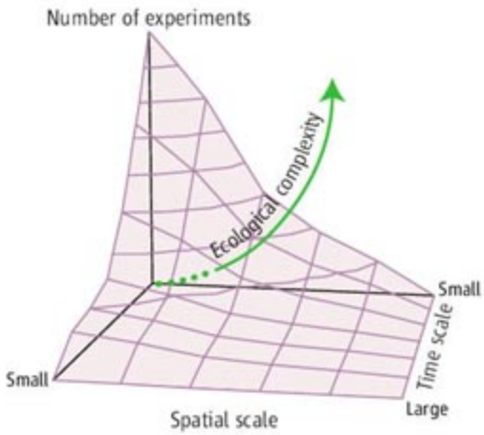
The experiment stands out for several reasons. First, the 5-year time span of the experiment underlines the importance of experimental duration for drawing the right conclusions. The lifetime of experimental research rarely exceeds 2 to 3 years (*3*–*5*) (see the figure), although the manipulated system may need longer for the transition from initial disequilibrium to new equilibrium conditions. A field experiment in Arctic tussock tundra showed that focusing on individual species' responses over the short term (3 years) gave poor predictions of their long-term (9 years) response (*6*). Carbon dioxide (CO_2) enrichment experiments in established forest stands revealed that the stimulation of above-ground growth of forest trees in the first years was a temporary effect and was followed by a time-dependent (in this case 4 to 5 years) adjustment of the growth regime back to almost the same level as before CO_2 enrichment (*7*). Hence, the observed effects of manipulation depend heavily on the time period of data evaluation and suggest different interpretations.

In the grassland experiment by Suttle *et al.*, the initial strong response of nitrogen-fixing forbs (that is, nongrass flowering plants with nonwoody stems) in the first few years was reversed through feedback processes, and the forbs were replaced by annual grasses, with consequences for both biodiversity and food web structure (*2*). Again, evaluation of the experiments after the first few years would have resulted in different trends and misleading inferences compared to those revealed in the longer run.

A second interesting feature of the Californian grassland experiment is how the projected precipitation regimes were implemented. Long-term mean precipitation is a useful indicator of the intensity of the hydrologic cycle, but the temporal and spatial patterns of the precipitation regime are the most important issues in determining impacts of



Not to scale. Ecological complexity increases with scale, whereas the number of ecological experiments shows the opposite trend. There is a strong tendency to ignore possible complicating factors of ecological complexity operating over a larger scale. This schematic chart is based on (*11*, *12*).

precipitation changes (*8*). In the grassland experiment, effects of increased rainfall depended strongly on the seasonality of the increase. Communities experiencing additional watering during the wet winter season responded similarly to those exposed to ambient rainfall, whereas watering at the end of the rainy season led to substantial and sustained changes in the composition of the affected communities (*2*). Hence, different temporal treatments representing the same trend of increases in annual precipitation, but with different seasonal patterns, highlighted the importance of the timing of rainfall.

There is a third reason for interest in these results. Although it is generally agreed that climate change will affect the temporal and spatial association between species interacting at different trophic levels, many studies concentrate on the effects of a single variable on a particular species. Thus, there is a strong tendency to ignore possible complicating factors operating over larger scales and/or multitrophic levels (*4*, *9*). Long-term field data from grassland habitats in Germany indicate that different trophic levels respond differently to climate fluctuations and suggest that differential trophic responses are likely to be a common, widespread, and important phenomenon (*10*). The community-level interactions considered in the experiment by Suttle *et al*. were strongly influenced by persistent altered environmental conditions and not a consequence of short-term fluctuations of the precipitation regime. The initial signal of increased plant species richness and greater diversity and abundance of invertebrate herbivores, predators, and parasitoids was reversed in the course of the experiment as a result of the increasing share of annual grasses with low nutritional value and monocultures of these plants offering low structural complexity. This finally led to a simplification of the grassland community as a whole (*2*).

Together, these examples warn against overstating the results of inappropriate experimental conditions in terms of temporal [and also spatial (*4*, *11*)] scales (see the figure). Careful interpretation of experimental data is thus crucial to avoid overinterpretation of early experimental results. In general, time-series analysis should be performed over as many years as possible.

The study by Suttle *et al*. shows how one can tackle ecological complexity in manipulative experiments: The 5-year duration of the experiment has revealed reversal trends of initial effects; different temporal patterns of treatment highlight the importance of the timing of rainfall compared to the annual amount; and feedback processes through higher trophic levels may overturn direct climatic effects on the species level and reverse community trajectories. These aspects make this work particularly valuable for ecological experiments and for global change research in general. It is a strong reference for the importance of field-based long-term monitoring and experiments for climate impact studies.

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CELL SIGNALING

Mitochondrial Longevity Pathways

György Hajnóczky and Jan B. Hoek

A cytosolic protein that translocates into the mitochondria may serve as an integration point for signaling pathways that control longevity and cell death.

The quest for longevity has led to the discovery of several genes that affect the life span of organisms ranging from yeast to mammals. An increased life span has been linked to the expression of sirtuins, impaired function insulin receptor homologs, and absence of the signaling protein $p66^{Shc}$. Several cell signaling pathways associated with these factors converge on the Forkhead/FOXO family of transcription factors, which regulate the expression of a battery of stress response proteins that affect antioxidant capacity, cell cycle arrest, DNA repair, and apoptosis (*1*). Life span–regulating proteins also directly affect mitochondrial function, including energy metabolism and reactive oxygen species production, in which $p66^{Shc}$ plays a critical role. How these mitochondrial processes integrate with the upstream signaling events to control life span has remained enigmatic. On page 659 of this issue, Pinton *et al*. describe a signaling pathway that controls the mitochondrial activity of $p66^{Shc}$ (*2*) (see the figure) and provides insight into how this integration might occur.

The extended life span of mice lacking $p66^{Shc}$ has been correlated with a decrease in mitochondrial metabolism (*3*) and reactive oxygen species production (*4*). Pinton *et al*. show that $p66^{Shc}$ is required for early mitochondrial responses to an oxidative challenge (hydrogen peroxide, H_2O_2). These responses include mitochondrial fragmentation and suppression of Ca^{2+} signal propagation to the mitochondria, followed by execution of apoptosis (cell death) in murine fibroblasts. The authors found that early mitochondrial response to H_2O_2 increased progressively with cell culture age, and used this model to map the signaling cascade through which $p66^{Shc}$ affects mitochondria.

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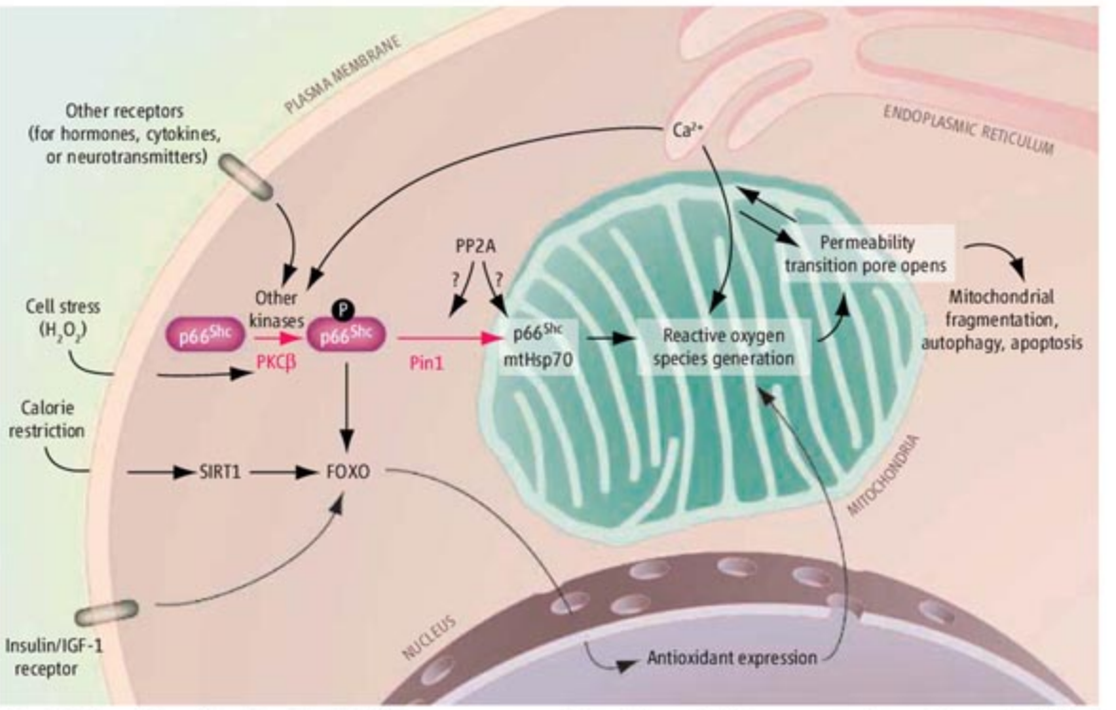
Reactive oxygen species affect the activity of many protein phosphatases and kinases. Phosphorylation of $p66^{Shc}$ on Ser^{36} can be mediated by several protein kinases and is indispensable for life-span regulation by $p66^{Shc}$. Pinton *et al.* show that inhibiting or silencing protein kinase C β protects cells against H_2O_2 challenge. Furthermore, overexpression of protein kinase C β reproduces the mitochondrial fragmentation and Ca^{2+} signaling defect in cells expressing $p66^{Shc}$, but not in cells lacking $p66^{Shc}$. Cells expressing a mutant form of $p66^{Shc}$ ($p66^{Shc}S36A$) that cannot be phosphorylated also lack the early mitochondrial response to protein kinase C β activity, indicating a requirement for $p66^{Shc}$ phosphorylation. Thus, there is remarkable interdependence between protein kinase C β and $p66^{Shc}$ in the mitochondrial response to oxidative challenges. Although H_2O_2 challenge seems to employ only protein kinase C β to phosphorylate $p66^{Shc}$, this step may serve as an integration site for multiple protein kinases activated by cell surface receptors.

$P66^{Shc}$ localizes predominantly in the cytoplasm, with a smaller fraction (10 to 40%) in the mitochondrial intermembrane space (*3*, *5*). The protein lacks a conventional mitochondrial targeting sequence, but its association with the mitochondrial TOM/TIM import complex and the mitochondrial heat shock protein mtHsp70 has been reported (*5*). Pinton *et al.* put forward the original idea that phosphorylation of Ser^{36} induces translocation of phosphorylated $p66^{Shc}$ to the mitochondria. They also provide evidence that both H_2O_2 challenge and protein kinase C β activation promote binding of $p66^{Shc}$ to Pin1, causing this translocation. Pin1 is a peptidyl-prolyl isomerase that induces cis-trans isomerization of phosphorylated Ser-Pro bonds. This confers phosphorylation-dependent conformational changes in Pin1 targets. Pin1 has been studied in the context of the processing of phosphorylated proteins in Alzheimer's disease (*6*), but the present data suggest that it has broader importance. Binding of phosphorylated $p66^{Shc}$ to Pin1 may expose a hidden sequence that targets $p66^{Shc}$ to the mitochondria. It is possible that this unconventional targeting mechanism might enable $p66^{Shc}$ to interact with a specific subset of a heterogeneous mitochondrial population, and provide a means for differential regulation of mitochondria by $p66^{Shc}$.

Activation of mitochondrial $p66^{Shc}$ requires its dephosphorylation and dissociation from mtHsp70, but it remains unclear as to whether dephosphorylation by the phosphatase PP2A occurs before, upon, or after translocation into the organelle. Once in the intermembrane space, $p66^{Shc}$ interacts with reduced cytochrome c to produce H_2O_2, which can promote opening of the mitochondrial permeability transition pore. The sensitivity of the suppression of mitochondrial Ca^{2+} signaling and fragmentation to inhibitors of the permeability transition pore shows that these effects of $p66^{Shc}$ are downstream of the pore opening. Interestingly, H_2O_2 formation in the mitochondria is required for pore opening even when cells are exposed to an H_2O_2 challenge. Perhaps $p66^{Shc}$-mediated reactive oxygen species generation requires a favorable environment in the intermembrane space to convert H_2O_2 to more damaging hydroxyl radicals and/or provide access to hidden sulfhydryl groups that regulate the permeability transition pore (*7*).

How is permeabilization of the mitochondrial inner membrane associated with onset of the aging phenotype? In the model of Pinton *et al.*, $p66^{Shc}$ supports an apoptotic response to a massive oxidative challenge, a classical consequence of permeability transition pore opening and the ensuing release of cytochrome c. Apoptosis and removal of seriously damaged cells may play a role in both extending and shortening the cell's life span. Apoptosis involves the entire mitochondrial population displaying a coordinated response throughout the cell (*8*). However, pore activation confined to a subpopulation of mitochondria could help remove impaired mitochondria by triggering their disposal by autophagy and degradation in lysosomes (*9*). Indeed, aging may be associated with impaired autophagy (*10*) and inhibiting autophagy prevents life-span extension in the nematode *Caenorhabditis elegans* (*11*). Thus, $p66^{Shc}$-dependent mitochondrial fragmentation and suppression of Ca^{2+} uptake may be relevant to localize and attenuate mitochondria damage where reactive oxygen species are produced as part of a mitochondrial quality control mechanism. Mice lacking $p66^{Shc}$ apparently remain healthy in the laboratory setting (*12*), but their sensitivity to environmental stress remains to be established. Thus, $p66^{Shc}$ may protect the organism against stress, but if targeted destruction of mitochondria by $p66^{Shc}$ overwhelms the autophagy capacity of the cell, this would set the stage for the accumulation of unprocessed oxidative-damaged cell constituents, a classical correlate of aging.

This conclusion suggests that regulating autophagy of damaged mitochondria may constitute another piece of the aging puzzle. The serine-threonine kinase mTOR is a critical inhibitor of autophagy (*10*) and also enhances mitochondrial metabolism and reactive oxygen species generation (*3*). Therefore, $p66^{Shc}$ and mTOR may interact to integrate multiple aspects of cell homeostasis that are relevant for aging. Sirtuins also may affect mitochondrial function beyond the expression of FOXO-regulated antioxidant and proapop-



Signal integration. Phosphorylated $p66^{Shc}$ may serve as an integration point for many signaling pathways that affect mitochondrial function and longevity. The pathway described by Pinton *et al.* is marked in red. Protein kinase Cβ (PKCβ).

totic proteins. Notably, PGC-1α, a transcriptional coactivator that controls mitochondrial biogenesis and energy metabolism, is regulated by the sirtuin SIRT1. Also, several sirtuins localize to mitochondria where they affect critical metabolic functions (*13*–*15*). SIRT1 and other life span–controlling proteins also have direct links to the mitochondrial permeabilization and autophagy, perhaps through Bcl-2 family proteins (*14*).

The factors that set the stage for the mitochondrial contribution to the aging process include inputs from different directions. Reactive oxygen species production in mitochondria is regulated by metabolic activity, substrate supply, and mitochondrial membrane potential. Superimposed on this background, mitochondrial import of $p66^{Shc}$ can provide an additional reactive oxygen species–producing element to trigger a local permeability transition pore opening that (together with other inputs) controls life span. Of course, this does not exclude a role for mitochondrial $p66^{Shc}$ in normal cell management of stress and damage repair. In fact, a recent study showed that $p66^{Shc}$ is highly expressed in fibroblasts from centenarians (*16*). $P66^{Shc}$ may well keep us fit while helping us age.

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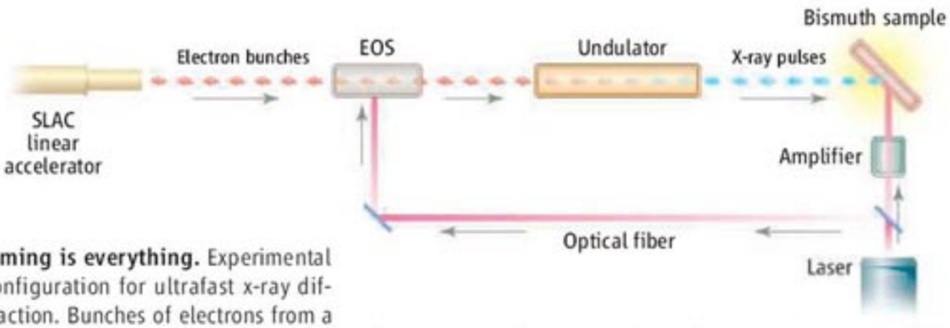
CHEMISTRY

Watching Atoms Move

The X-ray free-electron laser has made possible a direct test of potential energy surface models for highly excited states of bismuth.

Joel D. Brock

For more than a century, x-ray diffraction has provided detailed information on the structure of matter on atomic length scales. The recent advent of high-energy x-ray free-electron lasers (XFELs) now provides researchers the ability to watch matter move on both atomic length and time scales. On page 633 of this issue, Fritz *et al.* (*1*) report the use of ultrashort x-ray pulses from an XFEL to measure the dynamics of atomic vibrations in bismuth when excited by photons. These measurements provide researchers direct tests of calculations of highly excited electronic states and provide basic insights into our fundamental understanding of condensed matter.



Timing is everything. Experimental configuration for ultrafast x-ray diffraction. Bunches of electrons from a linear accelerator enter an XFEL undulator that generates short x-ray pulses. These are used to create diffraction patterns of the bismuth foil, which is heated by pulses from a laser. Electro-optic sampling (EOS) is used to detect the relative position in time of the x-ray and laser pulses, so that changes in bismuth lattice vibrations can be determined precisely.

Our understanding of the static or time-averaged structure of matter on atomic length scales has been dramatically advanced by direct structural measurements with x-rays. The current technical capability of x-ray crystallography is immense. The cover of *Science* regularly displays the structure of biologically important macromolecules determined through x-ray crystallography, and it is not unusual for these structures (e.g., viruses) to contain millions of atoms. However, the structure of matter is not static. Developing our understanding of the fundamental behavior of matter requires structural measurements on the time scales on which matter moves.

There are several important physical time scales of interest. Conformational relaxations in molecular systems and electron-lattice energy transfer in crystalline solids typically occur in a few picoseconds. Faster still are atomic vibrational periods, which are typically on the order of 100 femtoseconds. The characteristic time scale for electron-electron collisions in solids is on the order of 10 femtoseconds. And, quickest of all, are correlations in the dynamics of interacting electrons, which typically decay in less than 1 femtosecond. The key feature of all these time scales is that they are all "ultrafast"; that is, a few picoseconds or shorter.

To date, ultrafast science has been the domain of femtosecond lasers operating at ultraviolet to infrared (IR) wavelengths. These wavelengths are not short enough for structural studies on atomic distances, and they are able to probe only those electronic states that extend over multiple atoms. However, building a suitable "hard" x-ray source (i.e., one that emits photons with wavelength in the range 1 to 2 angstroms, or an energy of about 10 keV) represents a major challenge.

For the past 35 years, the intense and highly collimated hard x-ray beams produced by synchrotron sources have been enormously successful both for static structural studies and for time-resolved studies down to the subnanosecond range. However, it is very difficult to create a useful ultrafast x-ray pulse with a conventional synchrotron because the equilibrium nature of an electron storage ring limits the electron-bunch length to the 10-picosecond range. Using state-of-the-art accelerator technology to "slice" the electron beam, researchers can generate ultrafast x-ray pulses (e.g., 200 femtoseconds) (*2*–*4*). The result is an ultrafast pulse of hard x-rays, but the slicing technique uses only a small fraction of the electrons in the bunch, dramatically reducing the flux. Consequently, there is a

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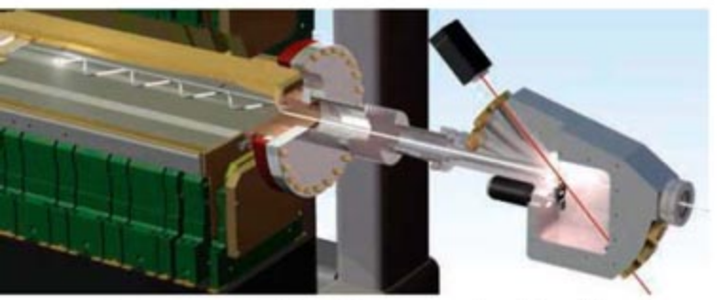
large worldwide effort to build linear accelerator (LINAC)–based ultrafast x-ray sources such as an XFEL or an energy recovery LINAC (ERL). XFEL and ERL sources circumvent the equilibrium electron-bunch size by using a LINAC rather than a storage ring.

Fritz *et al.* report femtosecond x-ray diffraction measurements performed at the Sub-Picosecond Photon Source (SPPS) at the Stanford Linear Accelerator Center (SLAC). The SPPS was a prototype XFEL built using the 2-mile-long LINAC at SLAC. These data represent the first real experimental glimpse into the behavior of materials at both atomic length and time scales. In their experiment, an ultrafast near-IR laser pulse photoexcites charge carriers in a bismuth crystal, which in turn excite one of the vibrational modes of the lattice—in this case, a coherent optical phonon (see the first figure). In essence, the nonequilibrium charge distribution abruptly alters the interatomic potential energy surface, thereby creating the force that drives the atomic motion. The dynamics of the resulting vibrational mode are determined by the shape of the nonequilibrium potential energy surface. Thus, by measuring the dynamics of the lattice motion, Fritz *et al.* are able to determine the (quasi)-equilibrium position and curvature of the interatomic potential.



X-ray stopwatch. The relative temporal position of the electron bunches (white) interacts with an electro-optic crystal which, in turn, imprints a polarization transient on the laser (red) pulse.

From a chemical point of view, having a fundamental understanding means understanding the adiabatic energy surface on which the constituent atoms move about during a chemical reaction. This is a very similar situation. We are watching the atoms move about after abruptly changing the potential energy surface. Thus, this experiment provides a clean, quantitative test of our current fundamental understanding of the interatomic potential energy surface of a highly excited atom as predicted by density functional theory.

On their way to making these measurements, the experimenters achieved several very important technical advances. The first was building and operating the SPPS. The second addressed a long-standing issue for pump-probe experiments with XFELs. One of the features of current XFEL designs is the generation of intense x-ray pulses by the self-amplified spontaneous emission (SASE) process. In SASE, density fluctuations in the electron bunch are amplified to make the pulse. Therefore, the pulses of x-rays vary in size, and there is no exact relation between the location of the electron bunch and the phase of the LINAC's radio frequency accelerating field. In this work, the researchers measured the arrival time of the x-ray pulse on a shot-by-shot basis with an electro-optic technique (*5*) (see the second figure). They then were able to use the pulse timing variation to obtain the relative delay between the pump laser pulse and the probe x-ray pulse, a vital piece of information in the experiments. Thus, they were able to turn what many predicted would be a major obstacle or challenge into a positive feature.

This clever use of XFEL beams will be critical to garnering the immense promise of these new sources. Chemists would like to make "movies" of reactions as molecules approach each other, form the intermediate transition states, and then relax into final products. Materials scientists would like to study the dynamics of events during thin-film deposition. Condensed matter physicists would like to study the lowest-energy excitations of unusual systems such as high-temperature superconductors, heavy fermion systems charge- and spin-density wave systems (fractional), quantum Hall systems, and colossal magnetoresistance systems. And, of course, the grandest challenge of all is to understand in detail the electronic, structural, and chemical processes involved in photosynthesis.

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CHEMISTRY

Coherence and Symmetry Breaking at the Molecular Level

Contrary to expectation, when an electron leaves a symmetric dihydrogen molecule before dissociation, the breakup is asymmetric. This paradox can be understood by considering fundamental properties of interacting waves.

Andrei Sanov

Coherence is the ability of waves to combine their oscillations in a defined, nonrandom fashion. It is a cornerstone of wave interference, such as when water waves join in one large swell on the ocean surface or when light waves are generated in lockstep to form a bright laser beam. In quantum mechanics, all particles behave like waves, and coherence is therefore a universal concept determining the fundamental properties of matter.

Coherent effects are most obvious when the interfering waves are restricted by symmetry. For example, electrons in molecules are described by coherent combinations of orbitals from different atoms. In symmetric molecules, the contributions of equivalent atoms to the bonding are limited to equal amplitudes, resulting in symmetric electron density distributions. However, in some cases, coherence can undermine symmetry, resulting in asymmetric spectral line shapes (*1*) or product distributions. To examine how this can happen, one may start by asking whether it is possible to distinguish two ends of a homonuclear diatomic molecule such as H_2.

The very premise may appear absurd: It seems to violate not only molecular symmetry, but also the fundamental indistinguishability of identical nuclei. Yet, on page 629 of this issue, Martín *et al.* report asymmetric electron emission from H_2, followed by asym-

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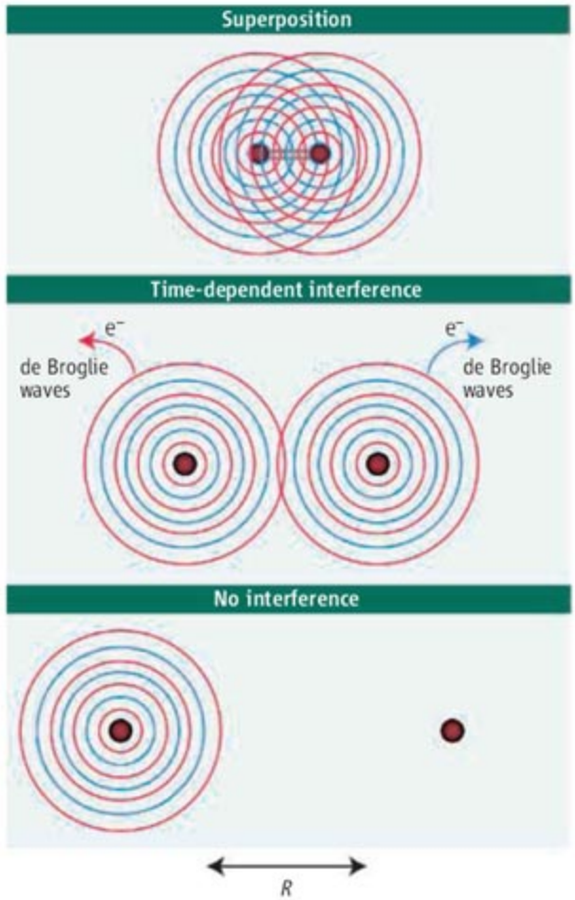
metric dissociation of the remaining molecular ion to a proton and a hydrogen atom (*2*). The dissociative ionization thus breaks the inversion symmetry both of the H_2 molecule and of the incident linearly polarized light.

The photoelectron distributions that lack inversion symmetry with respect to the molecular center of mass can be observed only because the two ends of the ironized molecules are ultimately distinguished by the different charge states of the final fragments, H and H^+. Even so, the result is counterintuitive, especially if one expects the ionization merely to eject an electron from the lowest-energy orbital of H_2. This orbital is symmetric with respect to inversion, that is, it is said to be of *gerade* (even) parity. Since quantum mechanics requires the electron parity to change upon the absorption of a single photon, the departing electron will be described by an *ungerade* (odd) wave function, corresponding to a perfectly symmetric photoelectron distribution.

This description is based on two oversimplifications. First, it assumes that the two electrons are completely independent from each other, and that the emitted and remaining electrons thus cannot exchange parity. Second, it decouples the ionization and dissociation processes by not taking into account the excited states of H_2, which contribute by way of delayed autoionization.

As discussed by Martín *et al.*, electron waves of both *ungerade* (odd) and *gerade* (even) parity are in fact emitted from H_2 via multiple direct and indirect ionization channels (*2*). A combination of odd and even functions is, in general, neither odd nor even. Thus, interference of the *gerade* and *ungerade* waves yields an asymmetric photoelectron distribution, which generally favors one or the other end of the molecule. This implies that the two nuclei in the remaining H_2^+ are no longer equivalent and the probability of charge localization on either one of them may differ from 50%.

To put this asymmetry in context, consider the dissociation of a homonuclear diatomic ion, either positive or negative, via a single channel of defined parity. As it falls apart, X_2^+ or X_2^- will retain its parity and symmetric charge distribution, $X^{\pm 1/2}...X^{\pm 1/2}$, until the loss of coherence due to external perturbations causes the charge to localize on one atom or the other. (Coherence is not really "lost," but transferred to a larger system including the perturbing fields.) Until then, the dissociating ion can be viewed as a coherent superposition of the localized-charge states.



Molecular interferometer. In the ionization of a homonuclear diatomic molecule, the photoelectrons are superpositions of waves emitted from two equivalent atoms (**top**). When photoionization is used as a probe of dissociation, the atoms separate at a speed determined by the reaction energetics, giving rise to time-dependent interference (**middle**). At large separation R, the interatomic coherence is lost and the photoelectrons are emitted from one or the other atom, without interference (**bottom**). Blue and red colors indicate wave crests and troughs, respectively.

This description is reminiscent of the famous double-slit experiment (*3*), in which electrons pass through a partition that has two openings. The electrons hit a screen and create an interference pattern, but we do not know which path the particles take. If we ascertain the path, the interference pattern disappears. In the case of the diatomic ion, the charge remains coherently delocalized, similar to the electron passing through both slits at once, unless a measurement is performed to resolve one of the two possibilities. The asymmetric fragment states in the dissociative ionization of H_2 can be described as superpositions of the localized-charge states with differing amplitudes, corresponding to slits of unequal width. The measurement of the H^+ recoil direction effectively identifies the charged fragment, similar to determining which of the two slits an electron passes through in the double-slit experiment.

This parallel can be taken further. The ionization of any homonuclear diatomic molecule is naturally described in "double-slit" terms, as the superposition of waves emitted from two coherent atomic centers. This gives rise to a conceptual view of a molecular-scale interferometer (see the figure) with path lengths determined by the internuclear distance R.

As in any interference scenario, the experimental observables depend on R/λ, where λ in this case is the de Broglie wavelength of the emitted electrons. The importance of this parameter was recognized by Cohen and Fano (*4*), who predicted that the ionization cross sections of homonuclear diatomic molecules should depend periodically on R/λ. This conclusion has since been extended to more subtle observables, such as photoelectron angular distributions.

The dependence of angular distributions on R/λ has been observed in two different regimes: by varying the photon energy and hence the electron wavelength (*4*, *5*); and as a function of R in time-resolved dissociation (*6*, *7*). The second scenario corresponds to the dynamic molecular interferometer (see the figure), where photoelectrons are emitted coherently from two recoiling centers, as has been described recently in the photodissociation of I_2^- (*7*). The interference parameter R/λ in this case couples the molecular dissociation and electron emission dynamics via $R(t)$ and λ, respectively. The experiment also showed that the excess electron can remain coherently delocalized over large internuclear distances (tens of angstroms), providing a striking demonstration of the persistence of symmetry and coherence.

With modern experimental techniques, the collusion of symmetry and coherence can be scrutinized in a diverse range of elementary quantum processes. Quantum theory is thus being subjected to the most rigorous test imaginable, including the search for its possible limitations. These studies propel our understanding of chemical interactions and bonding, probing the driving force of chemical reactions—the electron dynamics.

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Mesoscale Iron Enrichment Experiments 1993–2005: Synthesis and Future Directions

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Since the mid-1980s, our understanding of nutrient limitation of oceanic primary production has radically changed. Mesoscale iron addition experiments (FeAXs) have unequivocally shown that iron supply limits production in one-third of the world ocean, where surface macronutrient concentrations are perennially high. The findings of these 12 FeAXs also reveal that iron supply exerts controls on the dynamics of plankton blooms, which in turn affect the biogeochemical cycles of carbon, nitrogen, silicon, and sulfur and ultimately influence the Earth climate system. However, extrapolation of the key results of FeAXs to regional and seasonal scales in some cases is limited because of differing modes of iron supply in FeAXs and in the modern and paleo-oceans. New research directions include quantification of the coupling of oceanic iron and carbon biogeochemistry.

The work of John Martin (*1*, *2*) sharply focused attention on the role of iron (Fe) in ocean productivity, biogeochemical cycles, and global climate by proposing "that phytoplankton growth in major nutrient-rich waters is limited by iron deficiency" (*2*). The candidate mechanism of Martin (*1*, *2*) points to the importance of changes, over geological time, in the magnitude of macronutrient uptake by phytoplankton in waters where macronutrient concentrations are perennially high (*1*). Specifically, Fe supply to the ocean was much higher during glacial maxima than at present (*1*), and it is estimated that the increase in Fe-induced productivity could have contributed perhaps 30% of the 80-ppm drawdown in atmospheric CO_2 observed during glacial maxima by enhancing the ocean's biological pump (*3*).

Early results from shipboard incubations in high nutrient–low chlorophyll (HNLC) waters presented compelling but equivocal evidence that phytoplankton growth was limited by Fe availability (*2*). After rigorous discussion, a consensus was reached (*4*) that, because shipboard experiments have artifacts, mesoscale Fe addition experiments (FeAXs) offered the best approach to resolve questions about the role of Fe in ocean productivity, C cycling, and climate. The main objective of FeAXs was to test whether Fe enrichment would increase primary productivity in HNLC waters, but additional questions focused on how Fe enrichment would affect nutrient use and export (*1*).

The era of mesoscale Fe enrichments started with IronEx I, where Fe and the conservative tracer SF_6 (*5*) were added to tropical HNLC surface waters (*6*). A further 11 FeAXs of similar design (*7*, *8*) in different HNLC regions (Fig. 1) later confirmed the capability to study pelagic ecology and biogeochemical cycling in a discrete water parcel over time and space scales of weeks and kilometers. Complementary approaches include ship-based observations of persistent blooms within HNLC waters (Fig. 1), termed here FeNXs (Fe natural enrichment experiments), that are driven by sustained and localized Fe enrichment (*9*).

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Common Findings in FeAXs

FeAXs have each used a common framework (*7*) that enables comparison of their biogeochemical signatures (Table 1 and tables S1 to S3). The results of FeAXs have substantially increased our understanding of ecological and biogeochemical dynamics and their interrelationships, and many findings are consistent with theory-based predictions of ecosystem dynamics. For example, they have shown that phytoplankton grow faster in warmer open-ocean waters (table S2), as predicted by algal physiological relationships (*10*), and that blooms across a range of FeAX sites display an inverse relationship between chlorophyll concentration and mixed-layer depth (Table 1), as forecast by theoretical relationships between light penetration and mixed-layer depth (*8*, *11*, *12*). More specifically, FeAXs have verified that Fe enrichment enhances primary production from polar to tropical HNLC waters (Table 1) and confirmed that Fe supply has a fundamental role in photosynthesis (photosynthetic competence, table S1), diatom sinking, Fe uptake rates (*13*), and other physiological processes. FeAXs have demonstrated reduced silica requirements of diatoms when relieved of Fe stress (*14*), confirming results from bottle experiments (*15*).

These mesoscale experiments have provided detailed time-series observations, within a tracer-labeled parcel of water [i.e., a Lagrangian framework (*7*)], of open-ocean blooms from initiation through evolution and decline (Table 1). Data collection within a Lagrangian framework gives unparalleled insights into bloom dynamics and clarifies how the interplay of factors such as initial conditions (table S1) and loss processes defines properties such as bloom magnitude, which exhibits a factor of 10 range in chlorophyll concentrations between FeAXs (Table 1). The broad suite of measurements and their high temporal resolution in FeAXs will be a useful tool to better interpret the less highly resolved observations available for naturally occurring blooms [e.g., the Antarctic Environment and Southern Ocean Process Study (AESOPS) (*16*)]. Furthermore, the high-resolution data sets have enabled the establishment of a mechanistic understanding, in some FeAXs, of the evolution, termination, and decline phases of blooms (*17*) (Table 1). The durations of these bloom phases provide an estimate of the lag time between the accumulation of phytoplankton C and its subsequent export (*17*); such an estimate has proved elusive in previous studies (*18*).

This experimental approach has presented a platform to examine in detail the interactions of top-down and bottom-up control—outlined in the ecumenical Fe hypothesis (*19*)—on phy-

toplankton community structure. For example, stocks of all phytoplankton groups increased initially upon Fe enrichment, but only the diatoms bloomed (Table 1) by escaping grazing pressure. Thus, unlike bottle incubations, FeAXs offer a holistic approach to studying the entire pelagic food web. This enables assessment of the interplay of ecological processes and the resultant biogeochemical signals, such as Fe-mediated increases in haptophyte abundances (table S2) and consequent faunistic shifts within the microzooplankton (*20*) (table S2) that lead to changes in dimethyl sulfoniopropionate (DMSP) (*20*) and dimethyl sulfide (DMS) concentrations (*20*) (Table 1), respectively. These changes in DMS concentration demonstrate that climate-reactive biogenic gases—in addition to CO_2—must be considered to obtain the cumulative effect of Fe enrichment on climate.

The scale of FeAXs, and in particular their use of the SF_6 tracer, enabled the construction of pelagic biogeochemical budgets for C (*17*) and Fe (*21*) under high-Fe conditions. FeAXs have permitted the study of whether speciation controls Fe bioavailability (*22*), the mechanisms behind changes in the production of Fe-binding ligands (FeBLs) in response to enhanced Fe (table S3), and other aspects of Fe chemistry. The SF_6 tracer has also helped demonstrate that the underlying physics at FeAX sites alters the bloom biogeochemical signature both by diluting phytoplankton stocks (Table 1) and by increasing the macronutrient inventory of the patch (table S3). Such patch dilution may result in experimental artifacts including arrested bloom development (*23*), which leads to reduced macronutrient uptake.

Together, the wide range of experimental conditions and resulting breadth of bloom signatures evident from FeAXs (Table 1 and tables S1 to S3) provide an essential data resource to improve existing ecological and biogeochemical models and to develop new ones. For example, a new model of DMS dynamics developed during Subarctic Ecosystem Response to Iron Enrichment Study (SERIES) provides a better understanding of how the complex interplay of physical, photochemical, and biological processes affects the temporal evolution of mixed-layer DMS concentrations (*24*).

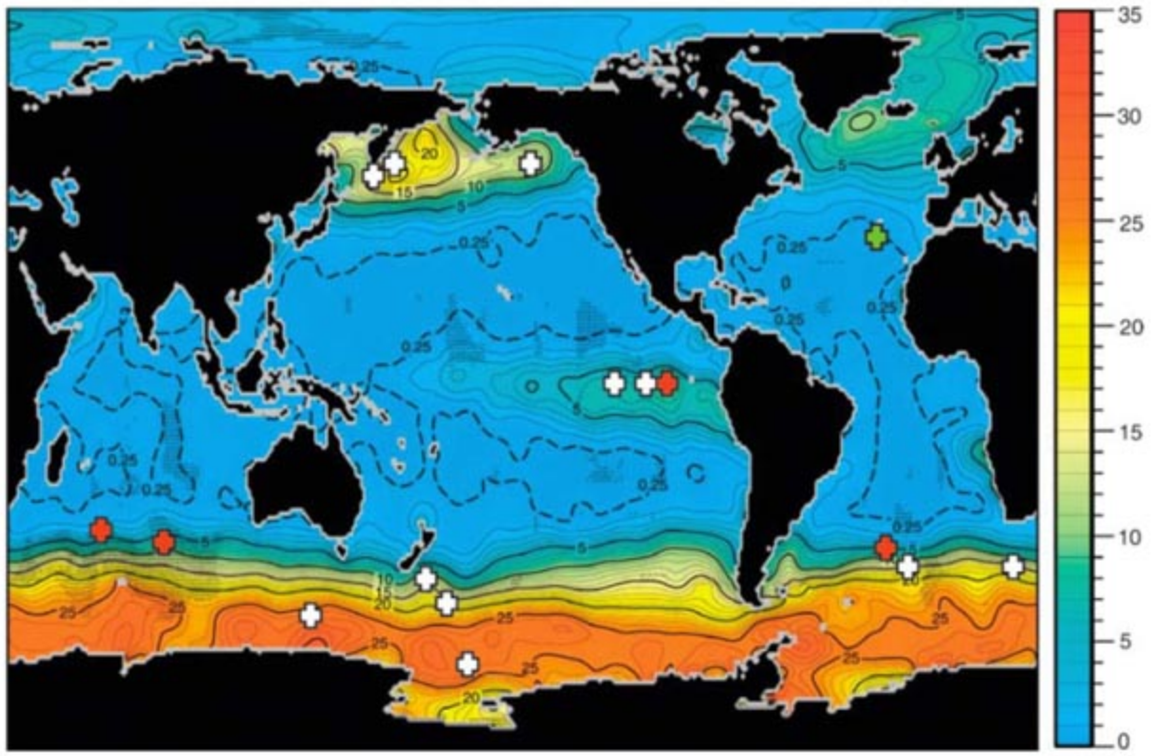

Fig. 1. Annual surface mixed-layer nitrate concentrations in units of μmol liter^{-1} (*48*), with approximate site locations of FeAXs (white crosses), FeNXs (red crosses), and a joint Fe and P enrichment study of the subtropical LNLC Atlantic Ocean (FeeP; green cross). FeAXs shown are SEEDS I and II (northwest Pacific; same site but symbols are offset), SERIES (northeast Pacific), IronEX I and II (equatorial Pacific; IronEX II is to the left), EisenEx and EIFEX (Atlantic polar waters; EIFEX is directly south of Africa), SOIREE (polar waters south of Australia), SOFEX-S (polar waters south of New Zealand), SOFEX-N (subpolar waters south of New Zealand), and SAGE (subpolar waters nearest to New Zealand). FeNX sites shown are the Galapagos Plume (equatorial Pacific), Antarctic Polar Front (polar Atlantic waters), and the Crozet and Kerguelen plateaus (Indian sector of Southern Ocean; Crozet is to the left of Kerguelen). For the geographical positions of the FeAXs, see (*8*). FeeP investigated whether N-fixing phytoplankton are simultaneously limited by Fe and P; see Table 1.

Scaling Up the Results from FeAXs

A key issue to be addressed is how natural or anthropogenic variability in Fe supply affects ocean biogeochemistry and global climate (*25*). FeAXs are relatively short-term experiments specifically designed to test whether Fe supply limits primary production in HNLC waters, and therefore they can address this issue only by extrapolation. Here, we consider whether findings from FeAXs can successfully be scaled up temporally (seasonal to geological) and spatially (regional to global). Four issues, addressed below, are central to tests of the validity of such extrapolation.

Macronutrient Uptake

The degree of Fe-mediated algal uptake of the mixed-layer macronutrient inventory will determine bloom longevity (*17*) and influence the magnitude of C sequestration (*1*, *3*). FeAXs, on a time scale of weeks, have exhibited a wide range of nutrient uptake (table S3), with depletion of >0.75 and >0.6 of the mixed-layer silicate and nitrate inventory, respectively, in several cases (table S2). Polar FeAXs, although of longer duration (Table 1), have resulted in <0.3 of the macronutrient inventory being used, although inventories at polar FeAX sites are greater than in other HNLC regions (table S2). Fe-mediated diatom blooms in both FeAXs (table S2) and natural conditions (*16*, *26*) can deplete silicate but not nitrate, which has led to bloom decline. SERIES suggests that both Fe supply and diatom species succession, as a result of decreasing silicate concentrations, set the silicate:nitrate uptake stoichiometry (*17*). Thus, although longer-term Fe enrichment (months) may result in uptake of a greater proportion of the macronutrient inventory, it is difficult to scale up the findings of FeAXs without information on the long-term stability of phytoplankton community structure, such as diatom species succession (*17*).

Mediation of bloom decline via macronutrient depletion means that grazer control of phytoplankton stocks is less likely on the shorter time scales typical of FeAXs. This may also apply in some cases to the Last Glacial Maximum, as abundant diatom resting spores from Southern Ocean sediment cores indicate substantial export from diatom blooms in the Atlantic sector triggered by nutrient exhaustion rather than grazer control (*27*). Thus, FeAXs may mimic naturally occurring blooms that are transient (weeks) and are terminated by rapid nutrient depletion with consequently little change in the grazer community (*17*).

Bloom Time Scales and Food Web Dynamics

FeAX blooms may be subject to zooplankton grazing (Table 1), which would result in less

efficient downward export of algal C (*20*) and an increase in pelagic Fe recycling (*28*). However, the generation times for grazers range from days (microzooplankton) to months (macrozooplankton), whereas FeAX blooms evolve over 2 to 3 weeks (Table 1). Increased microzooplankton and, in some cases, mesozooplankton abundances (Table 1 and table S2) and subsequent alteration of food web dynamics were evident during FeAX blooms (table S2). If FeAXs were of longer duration, would stocks of large zooplankton increase with sustained Fe-elevated productivity? If so, how would they influence the bloom signature? Heavy grazing pressure, exerted by macrozooplankton, occurs in some upwelling regions (*29*) where a continuous nutrient supply (months) maintains a high-productivity system. Recent FeNXs, at sites with sustained nutrient supply (*9*), will reveal whether such an adaptive grazer response occurs during long-term blooms within HNLC waters, and hence whether upscaling the results of FeAXs to sustained naturally occurring blooms (months) is valid. If such an adaptive grazer response is observed, the potential long-term biogeochemical feedbacks of grazer-mediated Fe recycling and reduced export efficiency of algal C should be explored via modeling simulations.

Modes of Iron Supply

Initial attempts to relate the Fe supply during FeAXs with that in the modern or paleo-ocean (*30*) were hampered by relatively poor understanding of Fe biogeochemistry. Since the mid-1990s, our understanding has advanced considerably through better estimates of the solubility (*31*) and upper ocean residence time of aerosol Fe (*32*), improved regional coverage of dissolved Fe (DFe) concentrations (*33*), and greater insight into the key role of FeBL in maintaining Fe in the upper ocean (*34*). Although measuring DFe remains challenging, many technical issues have now been addressed (*35*). Our improved understanding is reflected in better models of dust depositional fluxes (*25*), oceanic DFe distributions (*36*), and the impact of higher Fe supply to the paleo-ocean (*14*), providing a more realistic picture of Fe supply to HNLC waters both now and in the geological past (Fig. 2).

A comparison of modes of Fe supply in FeAXs, FeNXs, and naturally occurring perturbations (Fig. 2) reveals a wide range in the magnitude, chemistry, residence time, and spatial and temporal scales of Fe supply. Although the pulsed Fe enrichments during FeAXs are

Table 1. The main findings from the 12 FeAXs (in chronological order from left to right) conducted between 1993 and 2005 [for additional details, see (*8*)]. See tables S1 to S3 for further details of initial conditions, ecosystem structure, and biogeochemical responses. Light climate, defined as the mean irradiance available to phytoplankton in the mixed layer, was calculated according to $I = I_0[1 - \exp(-K_e z)]/K_e z$, where I is mean mixed-layer irradiance (PAR), I_0 is the subsurface PAR, K_e is the vertical light attenuation coefficient (m^{-1}), and z is the depth of the upper mixed layer. Dilution rate is the mean growth rate of the SF_6-labeled patch over the duration of each FeAX. Each property is expressed volumetrically but can readily be converted to a column integral by using the data on mixed-layer depth (MLD). Terms prefixed with a delta such as ΔDIC denote maximum minus initial concentrations; nc, no significant change (relative to the surrounding HNLC waters); blank cells indicate that no data are currently available. The ratio of maximum to minimum primary production is based on column integrals.

Property	IronEX I (*6*)	IronEX II (*30*)	SOIREE (*49*)	EisenEx (*56*)	SEEDS I (*57*)	SOFEX-S (*54, 58*)	SOFEX-N (*58*)	EIFEX (*46*)	SERIES (*17*)	SEEDS II (*59*)	SAGE (*59*)	FeeP (*59*)
Fe added (kg)	450	450	1750	2350	350	1300	1700	2820	490	480	1100	1840
Temperature (°C)	23	25	2	3 to 4	11	−1	5	4 to 5	13	9 to 12	11.8	21
Season	Fall	Summer	Summer	Spring	Summer	Summer	Summer	Summer	Summer	Summer	Fall	Spring
Light climate (μmol quanta m^{-2} s^{-1})	254 (max) to 230 (min)	216 to 108	59 to 33	82 to 40	178 to 39	103 to 62	125 to 74		173 to 73		59 to 52	
Dilution rate (day^{-1})	0.27	0.18	0.07	0.04 to 0.43	0.05	0.08	0.1		0.07 to 0.16			0.4
Chlorophyll, $t = 0$ (mg m^{-3})	0.2	0.2	0.2	0.5	0.9	0.2	0.3	0.6	0.4	0.8	0.6	0.04
Chlorophyll, maximum (mg m^{-3})	0.6	3.3	2.3	2.8	23.0	2.5	2.4	3.0	5.5	2.4	1.3	0.07
MLD (m)	35	40*	65*	80*	13	35	45	100	30*	30	70*	30*
Bloom phase (duration, days)	Evolving (5) subducted	Decline (17)	Evolving (13)	Evolving (21)	Evolving (10)	Evolving (28)	Evolving (27) subducted	Partial decline, evolving (37)	Decline (25)	Evolving (25)	No bloom (17)	No bloom (7)
δDIC (mmol m^{-3})	6	26	17	14	58	21	13		36		nc	<1
δDMS (μmol m^{-3})	0.8	1.8	2.9	1.3, then to 0†	nc	nc	Increased		8.5, then to −5.7†	nc	nc	nc
Dominant phytoplankton	Mixed	Diatom	Diatom	Diatom	Diatom	Diatom	Mixed	Diatom	Diatom	Mixed	Mixed	*Cyanobacteria Prochlorococcus*
Export	nc	increase	nc	nc	nc	Increase	Increase§	Increase	Increase	nc	nc	
Mesozooplankton stocks	Increase‡	Increase	nc	nc	nc	nc	nc	Increase	Increase	Increase	nc	nc
Primary production (max/min ratio)	4	6	9	4	4	6	10	2	10		2	1.7

*Changes in MLD were observed during the study; the maximum MLD is shown (for initial MLD, see table S1). †An initial increase in DMS concentration followed by a decline by the end of the study. ‡Based on anecdotal evidence. §Increased export was mainly associated with a subduction event.

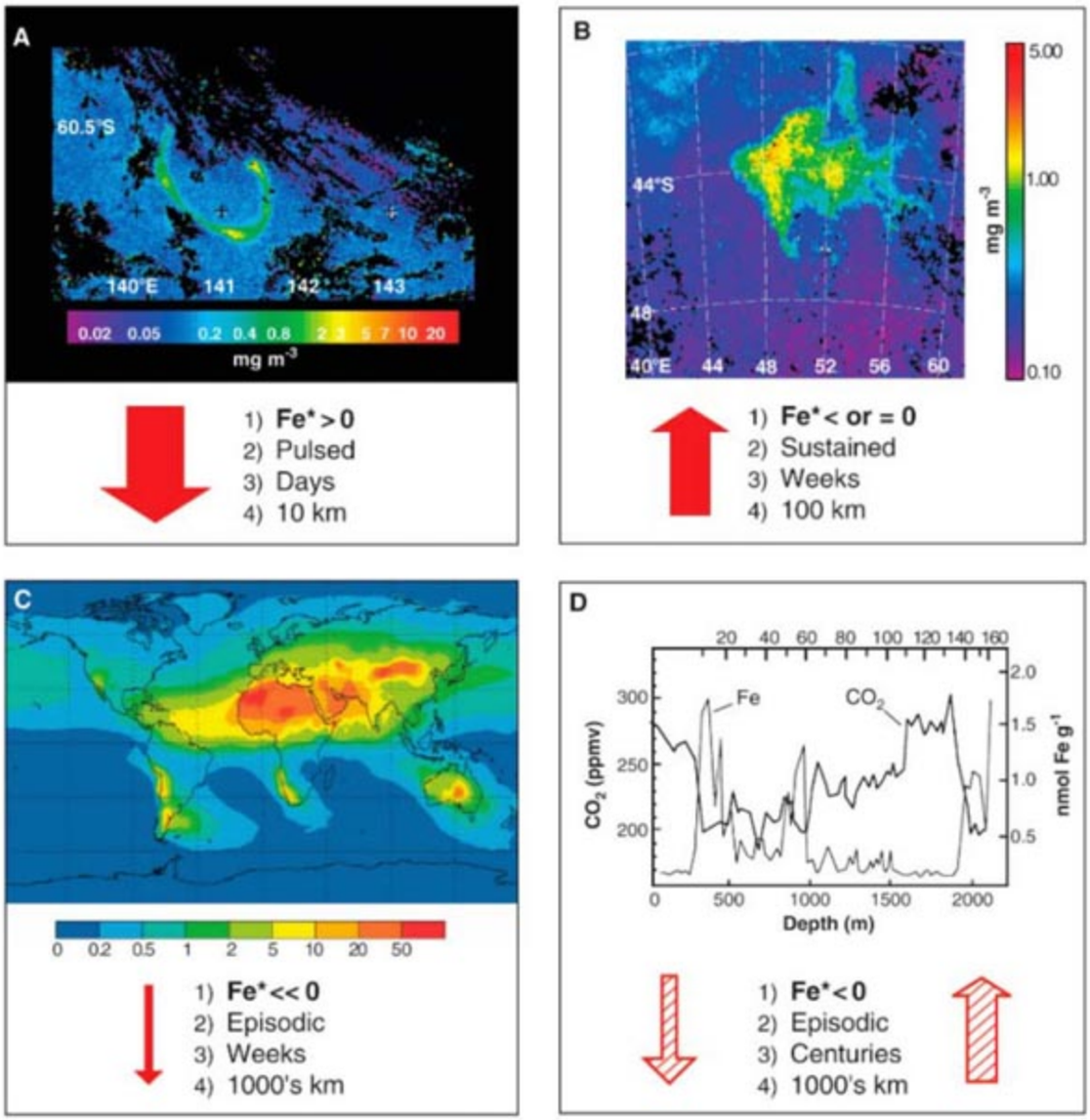

Fig. 2. A comparison for Southern Ocean waters of mechanisms responsible for perturbations in Fe supply. Numbers in each panel: 1) Fe*, the relative magnitude of Fe supply relative to macronutrient supply (*36*); 2) the mode of Fe supply; 3) the time scale over which surface waters receive increased Fe supply; and 4) the length scales of Fe supply events. (**A**) Satellite image of a purposeful in situ Southern Ocean FeAX [SOIREE (*49*)]. (**B**) An FeNX near Crozet within the HNLC Southern Ocean, where naturally occurring blooms are evident from remote sensing (*9*). (**C**) An atmospheric dust deposition event (dust units are g m^{-2} $year^{-1}$) in the modern Southern Ocean [e.g., from Patagonia (*25*)]. (**D**) Fe supply to the Southern Ocean during the glacial maxima from direct [i.e., higher dust deposition (*1*, *39*)] and/or indirect [i.e., upwelling of waters with higher Fe concentrations (*40*)] sources. The magnitude of this supply is unknown; hence, Fe* is expressed as < 0. Fe* is defined as Fe* = [Fe] − {(Fe/P) algal uptake ratio × [PO_4^{3-}]} (*36*). If Fe* > 0, primary production is ultimately macronutrient-limited; if Fe* < 0, production is ultimately Fe-limited. The width of red arrows denotes the relative magnitude of changes in Fe supply; the hatched arrows in (D) denote uncertainties about whether Fe supply in the geological past was episodic or sustained (see text). In (B) to (D), downward- and upward-pointing arrows represent atmospheric and oceanic (upwelling) supply, respectively. Consideration of Fe chemistry for each of these modes of supply is beyond the scope of this review, but see (*22*).

analogous to episodic dust events, the total Fe supplied in FeAXs is much larger, and Fe solubility is greater than from dust deposition [(*7*); see also (*31*)]. Also, there is little evidence of blooms (i.e., >1 mg chlorophyll m^{-3}) after episodic dust deposition into both HNLC (*37*) and low nutrient–low chlorophyll (LNLC) waters (*38*).

During the glacial maxima, increases in Fe supply are evident over a time scale of centuries (*1*). Aerosol Fe supply to the Southern Ocean during the glacial maxima was higher than at present by a factor of 10 (*1*, *39*). The magnitude of this supply is potentially comparable to that during FeAXs and FeNXs (Fig. 2). However, there are uncertainties about the mode of Fe supply during glacial maxima. Supply was either episodic and localized from dust storms [e.g., Patagonia (*39*)] and/or sustained and global, being driven by Southern Ocean upwelling and oceanic circulation (*40*) in conjunction with global dust deposition as the main Fe source (*14*). A major unknown in the geological past is the fate of Fe incorporated into phytoplankton blooms. Was dust-mediated Fe supply lost to the deep ocean as declining blooms sank [as aggregates (*23*)], or was it efficiently recycled by biota in the subsurface ocean and subsequently upwelled? Uncertainty over the fate of Fe is highlighted by comparing two modeling studies. They indicate that substantial atmospheric CO_2 drawdown resulted from the routes of high dust deposition with no Fe recycling (*41*) and from lower rates of dust deposition with recycling and subsequent upwelling (*14*). The pulsed Fe supply in FeAXs may therefore be more relevant to a paleo-ocean with episodic dust supply (weeks) and Fe export to the deep ocean, whereas FeNXs are a better proxy if Fe supply was sustained (months) by upwelling and recycling. Comparison of the results of FeAXs and FeNXs via modeling studies will provide insights into how different modes of Fe supply affect oceanic Fe and C biogeochemistry.

Coupled Iron-Carbon Biogeochemistry

The degree to which the biogeochemical Fe and C cycles are linked is central to determining the impact of increased Fe supply on atmospheric CO_2 drawdown and global climate in the geological past. A key parameter is the efficiency of phytoplankton C fixation per unit DFe [i.e., δ(POC formation)/δ(Fe supplied), where POC is particulate organic carbon], as the resulting δPOC export term will set the atmospheric drawdown efficiency [δ(air-sea CO_2 exchange)/δ(POC exported)]. Also, because Fe supply during the geological past was elevated for centuries (Fig. 2D), it is important to determine the fate of C relative to Fe in the upper ocean over longer time scales: Is Fe retained via remineralization in the water column or exported to the sediments? [i.e., δ(DIC remineralized)/δ(Fe remineralized) and δ(POC exported)/δ(PFe exported), where DIC is dissolved inorganic carbon].

There are few published data on Fe/C ratios for particle production, remineralization, or export (Fig. 3). A range of three orders of magnitude in Fe/C molar ratios is evident, which is probably due to the use of different approaches as well as actual differences in C and Fe biogeochemistry. This variability in Fe/C ratios has been

ascribed to a number of processes, such as differential remineralization of Fe and C on sinking particles [due to processes including scavenging on Fe (*36*, *42*)], which results in increased PFe/POC ratios with depth (Fig. 3). Also, phytoplankton in high-Fe surface waters may take up more Fe per unit of C fixed [i.e., "luxury" Fe uptake (*13*, *43*)], resulting in greater Fe remineralization than C remineralization on sinking particles relative to particles in HNLC waters (*33*). The available data on PFe/POC ratios indicate that settling particles from natural blooms (northeast Atlantic; Fe/C molar ratio 2.7×10^{-4}) and FeAXs (Fe/C molar ratio 3.1×10^{-4} to 2.1×10^{-3}) have higher ratios than those in HNLC waters (Fig. 3). During FeAXs, much of the Fe added is rapidly lost via precipitation and patch dilution (*21*); hence, Fe/C ratios from FeAXs will be overestimated by a factor of more than 2 (Fig. 3). Moreover, the time scales of FeAXs do not permit the fate of Fe (recycled or exported) initially added to the mixed layer to be assessed (*44*), and hence the ultimate efficiency of (Fe added):(C sequestered to depth) cannot be determined. Thus, upscaling the Fe:C stoichiometry from FeAXs to greater spatial and temporal scales is not currently recommended.

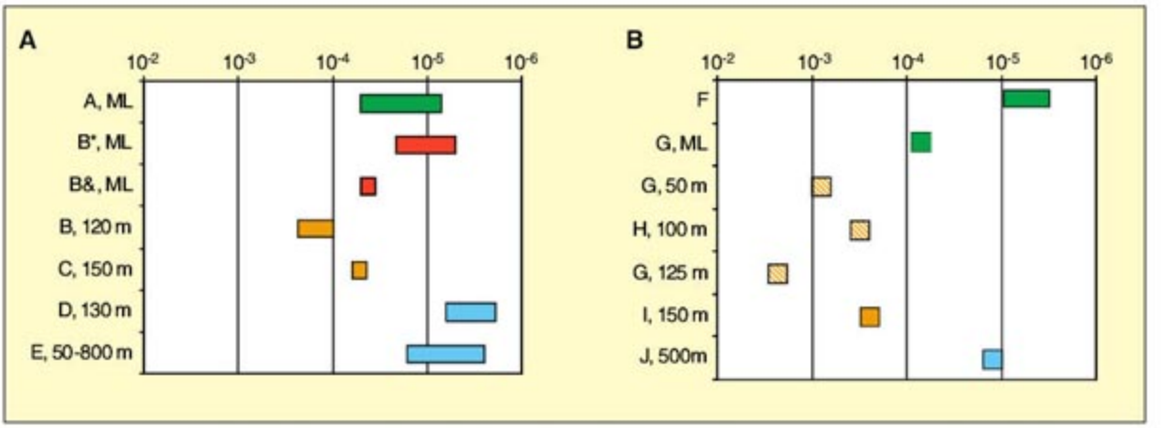

Fig. 3. Summary of published Fe/C molar ratios (on a log scale) from (**A**) low-Fe HNLC waters and (**B**) high-Fe waters and FeAXs (FeAXs denoted by hatched bars). Ratios were obtained from a range of sources: mixed-layer phytoplankton (green), suspended biogenic particles (red), sinking biogenic particles (brown), and remineralization of particles inferred from dissolved constituents (blue). Symbols in (A): A, Southern Ocean (*50*); B, subantarctic (*42*); C, subarctic Pacific (*51*, *52*); D, northeast Pacific (*1*); E, the low-Fe North Atlantic (*43*); ML, surface mixed-layer samples; *, biogenic Fe only; &, lithogenic and biogenic Fe. Symbols in (B): F, a ratio from an Fe-replete algal culture (*53*); G, SERIES (*17*); H, SOFEX-S (*54*); I, the northeast Atlantic (*51*);], the high-Fe North Atlantic (*33*). The ratios were derived from a wide range of approaches including algal lab cultures (*53*), sediment traps (*42*), vertical nutrient profiles in HNLC waters (*1*), and particle regeneration from apparent oxygen use versus DFe (*33*, *43*). Assessing the bioavailability of Fe (*22*) is a confounding factor in estimating Fe:C ratios, over and above the effect of patch dilution in FeAXs on the fate of the added Fe. The Fe/C ratios derived from FeAXs in (B) are (Fe added):(C exported) and assume that the Fe term is the total amount of Fe added, which may overestimate this ratio by 100% or more (*21*, *55*).

The Future: Key Questions and Approaches

Key findings from FeAXs offer insights for modelers, although a limited number of these findings can be extrapolated directly to regional and seasonal scales for Fe enrichment. Such limited extrapolation relates to limitations in the FeAX design (*7*) and to uncertainties in our understanding of Fe biogeochemistry in the paleo-ocean. Key questions center around the issues of macronutrient use, ecosystem responses, modes of Fe supply, and coupling of Fe-C biogeochemical cycles, for which we propose three hypotheses.

First, with respect to macronutrient uptake and ecosystem dynamics, we hypothesize that in addition to magnitude, the stoichiometry of macronutrient and Fe supply to HNLC surface waters is equally critical in determining whether blooms are transient (weeks) or sustained (months). This in turn will dictate the planktonic community that develops and the subsequent biogeochemical balance between Fe recycling within, and export from, the surface mixed layer.

Second, although the mode of Fe supply is important (Fig. 2), the factors that influence the availability of the Fe supplied to the biota are critical. We hypothesize that the magnitude of the Fe available to the biota will be determined by the mode of Fe supply and in particular by the subsequent mobilization and retention of this Fe by upper-ocean processes. For aeolian Fe supply, these processes include aerosol Fe mixed-layer residence time (*32*), photochemistry, FeBL concentrations (*25*) and their joint impact on aerosol dissolution, and the ability of bacteria to access lithogenic PFe (*42*). The bioavailability of Fe supplied from upwelling may be influenced by processes such as photochemistry or by the concentration and binding strength of the upwelled Fe and FeBL relative to those in the surface mixed layer.

Regarding the issue of Fe and C biogeochemistry, we offer a third hypothesis: that the relative importance of the processes that set particulate Fe/C ratios and their controlling factors will vary both regionally and seasonally. These processes, which will dictate Fe and C export, include algal Fe uptake and the differential rates of particle remineralization for Fe and C in surface and subsurface waters. Each of these, in turn, will be determined by a range of factors such as DFe concentration [algal Fe uptake (*43*)], food web structure and grazing activity [remineralization rates (*45*)], and particle properties and transformations including sinking rate or scavenging [export efficiency (*36*, *42*)].

Testing these hypotheses will require both specific and multistranded approaches that link FeAXs, FeNXs, and biogeochemical Fe and C studies in a range of locales. Three are advocated:

1) Modeling studies to apply our improved understanding of Fe biogeochemistry in the modern ocean to the geological past. Model simulations should also capitalize on the complementary approaches offered by FeAXs and FeNXs into how pulsed versus sustained Fe supply affects ecosystem dynamics and biogeochemistry.

2) Improved experimental designs to overcome the limitations of FeAXs, such as smaller and more frequent Fe doses, greater patch length scale (>>10 km), and additional measurements that provide insight into the impact of Fe enrichment on climate (e.g., biogenic gases) or Fe cycling (e.g., fate of Fe). Detailed comparison of the biogeochemistry of differing FeNXs would help us understand better the influence of a range of Fe:macronutrient stoichiometries on bloom dynamics and C biogeochemistry. Such experiments require application of both existing [aircraft, laser imaging detection and ranging (*46*)] and new [gliders, sensor arrays (*47*)] technologies, and should be linked to regional circulation models with embedded biogeochemistry. The utility of shipboard Fe enrichments to study algal physiology in detail should not be overlooked (*15*).

3) Biogeochemical studies to jointly measure key properties in the Fe and C cycles, such as Fe/C ratios and FeBL concentrations associated with particle transformations, will require specific investigation of end members—HNLC, LNLC, and high-Fe waters in coastal and offshore waters. These, in conjunction with the improved experimental designs described above, will provide insights into temporal and spatial controls on Fe/C ratios in both high- and low-Fe regimes.

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60. The workshop "A Synthesis of Mesoscale Iron-Enrichments," held in Wellington in November 2005, was supported by the Surface Ocean–Lower Atmosphere Study, NSF, NIWA, the New Zealand Royal Society, the UK Royal Society, Belgian Federal Science Policy, and the Natural Sciences and Engineering Research Council of Canada. We thank E. McKay and K. Richardson for the graphics, and two anonymous reviewers for their helpful comments and insights. This manuscript is dedicated to the memory of R.B.

Supporting Online Material

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Dimensions of Mind Perception

Heather M. Gray,* Kurt Gray, Daniel M. Wegner

What kinds of things have minds? Answers to this question often hinge on perceptions. Turing (*1*) held that a computer has a mind if a perceiver can't tell that it is not human, and Dennett (*2*) has proposed that every mind is defined as such in the eye of the beholder. But to date, it has generally been assumed that mind perception occurs on one dimension—things simply have more or less mind—and the dimensions of mind perception have remained unexamined. Studies testing whether chimpanzees perceive minds (*3*) and whether children or people with autism have this ability (*4*) use a variety of indicators but have not explored whether minds are perceived along one or more dimensions. We studied the structure of mind perception through 2399 completed surveys on the Mind Survey Web site (*5*).

Each survey called for 78 pairwise comparisons on five-point scales of 13 characters for one of 18 mental capacities (e.g., capacity to feel pain) or for one of six personal judgments (e.g., "which character do you like more?"). The characters included seven living human forms (7-week-old fetus, 5-month-old infant, 5-year-old girl, adult woman, adult man, man in a persistent vegetative state, and the respondent him- or herself), three nonhuman animals (frog, family dog, and wild chimpanzee), a dead woman, God, and a sociable robot (Kismet). So, for example, one such comparison involved rating whether a girl of 5 is more or less likely to be able to feel pain than is a chimpanzee. The survey samples were largely independent; 2040 unique respondents contributed data. Participants with many backgrounds responded but averaged 30 years of age and were modally female, white, unmarried, Christian, Democrat, and with some college education (*6*).

Mind perception dimensions were identified by computing character means for each mental capacity survey and submitting the correlations between capacities across characters to principal components factor analysis (varimax rotation). The rotated solution accounted for all 18 capacities (extraction communalities ranged from 0.82 to 0.99), explained 97% of rating variance, and yielded two factors with eigenvalues over 1.0. A factor we termed Experience (eigenvalue = 15.85) accounted for 88% of the variance and included 11 capacities (from highest loading): hunger, fear, pain, pleasure, rage, desire, personality, consciousness, pride, embarrassment, and joy. A second factor, Agency (eigenvalue = 1.46), accounted for 8% of the variance and included seven capacities: self-control, morality, memory, emotion recognition, planning, communication, and thought. Characters' factor scores on these dimensions (Fig. 1) reveal interesting features; for example, God was perceived as having much Agency but little Experience.

Personal judgments of the characters were related to the mind perception dimensions. Some judgments were related to both Experience and Agency and suggest that, with the progression from no mind (bottom left) to adult human mind (top right), characters become more highly valued. Thus, both dimensions correlated with liking for a character, wanting to save it from destruction, wanting to make it happy, and perceiving it as having a soul (r ranging from 0.38 to 0.72). Such integrated use of the dimensions in valuing minds can account for the traditional conceptualization of mind as perceptible along a single dimension.

However, the remaining judgments showed differing correlations with the two dimensions. Deserving punishment for wrongdoing ("If both characters had caused a person's death, which one do you think would be more deserving of punishment?") correlated more with Agency ($r = 0.82$) than Experience ($r = 0.22$, $z = 2.86$, $P < 0.05$), whereas desire to avoid harming ("If you were forced to harm one of these characters, which one would it be more painful for you to harm?") correlated more with Experience ($r = 0.85$) than Agency ($r = 0.26$, $z = 2.10$, $P < 0.05$). The dimensions thus relate to Aristotle's classical distinction between moral agents (whose actions can be morally right or wrong) and moral patients (who can have moral right or wrong done to them). Agency is linked to moral agency and hence to responsibility, whereas Experience is linked to moral patiency and hence to rights and privileges. Thus, our findings reveal not one dimension of mind perception, but two, and show that these dimensions capture different aspects of morality.

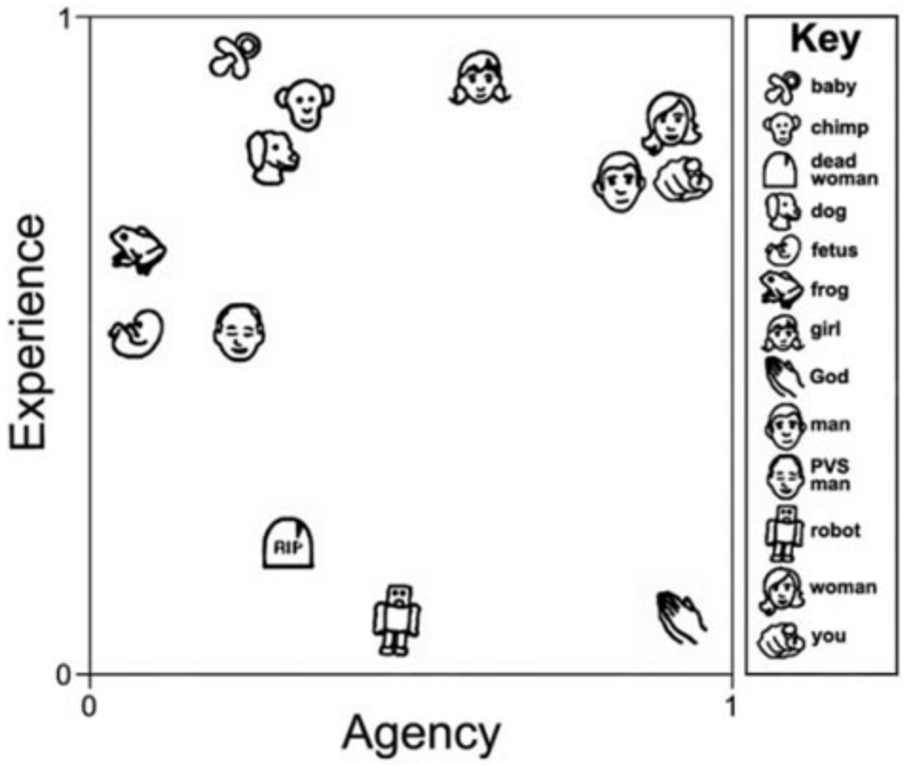

Fig. 1. Adjusted character factor scores on the dimensions of mind perception. PVS, persistent vegetative state.

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7. We acknowledge J. Bradshaw, J. Hromjak, K. Kassam, P. Piff, and B. Simpson and funding from National Institute of Mental Health grants MH-49127 and MH-71053 and from a Social Sciences and Humanities Research Council Fellowship.

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Composite Materials with Viscoelastic Stiffness Greater Than Diamond

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We show that composite materials can exhibit a viscoelastic modulus (Young's modulus) that is far greater than that of either constituent. The modulus, but not the strength, of the composite was observed to be substantially greater than that of diamond. These composites contain barium-titanate inclusions, which undergo a volume-change phase transformation if they are not constrained. In the composite, the inclusions are partially constrained by the surrounding metal matrix. The constraint stabilizes the negative bulk modulus (inverse compressibility) of the inclusions. This negative modulus arises from stored elastic energy in the inclusions, in contrast to periodic composite metamaterials that exhibit negative refraction by inertial resonant effects. Conventional composites with positive-stiffness constituents have aggregate properties bounded by a weighted average of constituent properties; their modulus cannot exceed that of the stiffest constituent.

In most elastic systems, a deformed object experiences a force with a component in the same direction as the deformation, so that the stiffness is positive. Negative structural stiffness (i.e., force/displacement ratio) can occur in pre-strained objects such as tubes buckled to form kinks, which contain stored energy at equilibrium (*1*). Experimentally, negative structural stiffness has been observed in lumped buckled systems composed of rubber tubes (*2*) and models of single foam cells (*3*).

The elastic modulus, a stress/strain ratio, is a measure of material stiffness. A negative modulus is anticipated in the context of Landau's (*4*) theory of phase transformation. As the temperature T is lowered from a value above the transformation temperature, an energy function of both strain ε and temperature (Fig. 1) with a single minimum gradually flattens, then develops two minima or potential wells. If the strain is a shear strain, the transformation is martensitic; for a hydrostatic strain, it is a volume-change transformation. The curvature of this energy function represents an elastic modulus, so that the flattening of the curve corresponds to a softening of the modulus near a critical temperature T_c, a phenomenon observed experimentally. Below T_c, the reversed curvature at a small strain represents a negative modulus. A negative modulus, in which the force that deforms an object is in the direction opposite to the displacement, is distinct from a negative Poisson's ratio, in which a material expands laterally when it is stretched (*5*–*7*). A negative modulus may occur in a pre-deformed object; it is then a negative incremental modulus. An object with all free surfaces and a negative modulus is unstable. A negative shear modulus causes bands or domains to form, even if the surfaces are constrained. A solid object with a negative bulk modulus (inverse compressibility) can be stabilized by a constraint of the surfaces (*8*), in contrast to fluids (*9*). Negative incremental compressibility has been observed in small-cell foams (*10*). Negative compressibility differs from negative thermal expansion (*11*), which is the stable contraction of an unconstrained object because of a temperature increase.

Negative stiffness can give rise to extreme values of physical properties in heterogeneous systems. For example, both negative stiffness and the resulting giant damping were observed (*2*) in a lumped system containing discrete buckled tubes. A composite with negative-stiffness inclusions is predicted to give rise to material properties greater than those of either constituent (*12*, *13*). Such behavior exceeds classical bounds (*14*), in which composite properties cannot exceed the properties of the constituents. These bounds are theorems assuming that each constituent initially contains no stored energy. Negative stiffness entails initial stored energy; viscoelastic dissipation, if present, enhances composite stability. In composites (*15*), anomalous high viscoelastic damping was observed and attributed to a negative shear modulus in ferroelastic inclusions that were partially constrained by the matrix. These inclusions were sufficiently small that some of them were single domains. Similar composites (*16*) of higher concentration exhibited instability, as predicted by a composite theory incorporating a negative shear modulus.

Composite materials were prepared with inclusions of barium titanate ($BaTiO_3$) in a tin matrix. $BaTiO_3$ was used because it is a ferroelastic, and also a ferroelectric, solid that exhibits a crystal volume change and a crystal shape change during phase transformations, specifically cubic-to-tetragonal transformations at T_c near 120°C and tetragonal-to-orthorhombic transformations near 5°C. The rationale for considering this class of phase transformation is that we can have a negative bulk modulus K in a constrained inclusion and yet still have stability. Constraint by the matrix restrains the transformation over a range of temperatures. Inclusions were, by design, sufficiently large to contain many domains below T_c. The bulk modulus of a material affects its stiffness in bending but not in torsion, because bending entails a local volume change.

Polycrystalline $BaTiO_3$ was fragmented and sieved to achieve a particle-size distribution between 210 and 150 μm. Domains in such materials can be smaller than 1 μm. Some particles were plated with nickel to improve their interface quality. Composites were fabricated using plated or unplated particles of the same pre-plated sizes. Dispersion of particle inclusions was achieved through an ultrasonic casting technique (*17*). Specimens (*18*) were sectioned from ingots, by means of a low-speed diamond saw, into rectangular

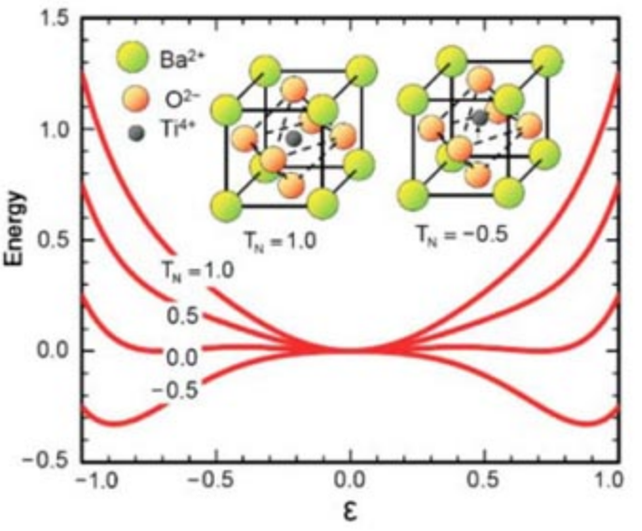

Fig. 1. Landau energy function (*18*) of strain ε and normalized temperature $T_N = (\alpha\gamma/\beta^2)(T - T_1) - 0.25$, with unit cells of $BaTiO_3$ in cubic and tetragonal phases. α, γ, and β are constants that depend on the material.

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cross sections, typically 2 mm × 2 mm × 3.5 cm, or they were cut into cylinders with diameters of 2.6 mm and lengths of 3 cm, by means of a wire electric-discharge milling machine. Digital optical micrographs of polished composite specimens were taken. Specimens were tested in bending by means of broadband viscoelastic spectroscopy (*19*). This instrument, which is capable of isothermal internal friction studies over 11 orders of magnitude in frequency, was modified to allow operation up to 300°C and to detect spontaneous strain exceeding 10^{-4}. The viscoelastic response was measured at 100 Hz in bending, which is well below any natural frequency. Torque was applied electromagnetically, and deformation was measured by a laser method. Temperature was monitored with a thermocouple in the air flow within 1 mm of the specimen, so as to avoid interference with viscoelastic measurement. Heating and cooling rates were 0.05 to 0.5°C/s. The procedure is typical of viscoelastic studies of materials, including those that undergo transformation.

Of the 13 specimens with plated inclusions, all exhibited an anomalous viscoelastic response in bending. An anomalous response is defined as a change in modulus or damping that is larger than could be accounted for by composite theory (*20*), assuming a positive inclusion modulus of any value between zero and infinity. Three specimens exhibited large anomalies and three exhibited a Young's modulus ($|E^*|$, absolute value of the complex viscoelastic modulus) greater than that of diamond. Because all materials exhibit some damping, any measured modulus is a viscoelastic modulus. Of the 15 specimens with unplated inclusions, 11 exhibited an anomalous response, and 1 exhibited a Young's modulus greater than that of diamond. It is theorized that the degree of the anomalous response depends on the quality of the inclusion/matrix interface. No anomalous behavior was observed in torsion. The microstructure of a specimen from the latter series, with inclusions measuring 10% by volume, is shown in Fig. 2. Modulus and damping (tan δ, with δ representing the phase between stress and strain) of this specimen are shown in Fig. 3. Given the modest damping, the magnitude of the modulus $|E^*|$ exceeds the real part E' by only about 2%. Young's modulus exceeds that of diamond over a narrow range of temperatures. Transient negative viscoelastic damping (tan δ) indicates the release of stored energy from the inclusions. Although they are stiff, these materials are not expected to be unusually strong or hard. Negative specific heat was observed in those specimens that exhibited the largest mechanical effects (*18*). This behavior is consistent with the negative bulk moduli of the inclusions because the theoretical specific heat depends on the constituent bulk moduli (*21*).

The behavior of all composites changed with thermal cycling, as was also observed in composites (*16*) with VO_2 inclusions; peaks tended to shift to higher temperatures and to attenuate with cycling. Composites with plated inclusions maintained their behavior over a greater number of cycles than did materials in which the inclusions were not plated. The inclusion/matrix interface is therefore clearly important in determining the behavior of the composites. Extreme elastic anomalies were observed for as many as five cycles in a particular specimen. Composite analysis (*13*) shows that macroscopic strain can be magnified locally by several orders of magnitude in the vicinity of the inclusions during the phase transformation. The macroscopic strain amplitude (less than 4×10^{-6} in these experiments) can therefore give rise to a local strain that is sufficient to cause yield in the tin matrix. This amplified local strain can account for the cycle dependence that could be ameliorated by using a stronger matrix.

Broad peaks in damping (tan δ) were also observed, as shown in Fig. 4. Even modest effects in these composites are notable because for a dilute particulate morphology, composite properties are known (*14*, *20*) to be relatively insen-

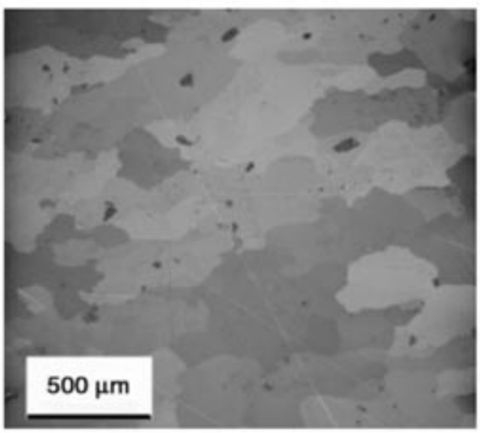

Fig. 2. Cross section of composite specimen in polarized light. $BaTiO_3$ inclusions appear as black spots. The polycrystalline structure of the tin matrix is shown in grayscale. Scale bar, 500 μm.

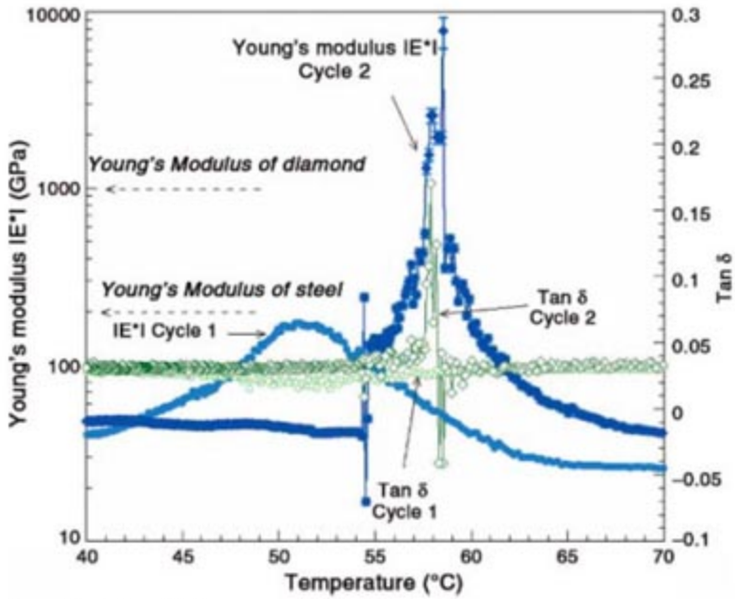

Fig. 3. Young's modulus $|E^*|$ and viscoelastic damping tan δ of the composite in Fig. 2, showing extremely high modulus over a range of temperatures. δ is the phase angle between stress and strain. Young's moduli of the constituents are $BaTiO_3$, 100 GPa; and tin, 50 GPa. Error bars (4%, smaller than data points) in the low-modulus regime are dominated by irregularity in the specimen diameter and in the high-modulus regime are dominated by digital resolution of the lock-in amplifier. Errors in tan δ, ~0.001, are smaller than the data points.

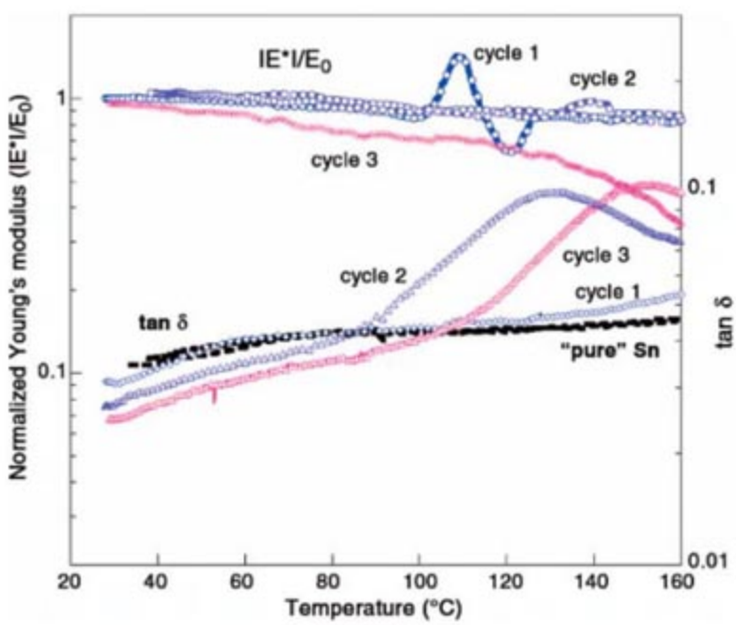

Fig. 4. Broad peaks in Young's modulus and viscoelastic damping (tan δ) of a composite similar to that in Fig. 2. E_0 is the normalizing modulus, which has a value of 30 GPa.

sitive to inclusion properties when they have a positive modulus. For example, with a 10% concentration of particles, the composite modulus $|E^*|$ due to infinitely stiff inclusions is predicted to increase by 22% as compared with that of the pure matrix. The composite damping due to inclusions with a peak damping $\tan\delta = 0.06$, corresponding to bulk $BaTiO_3$, is predicted to be only 6% greater than that of the matrix. The damping peaks shown in Fig. 4 (8% inclusion concentration) correspond to a factor of 2 increase as compared with pure tin (also shown), so, as with the above giant anomalies in the modulus, negative compressibility of the inclusions is inferred.

The present extreme-stiffness results are based on negative compressibility (inverse bulk modulus K, resistance to volume change) of inclusions, in contrast to the negative shear modulus G (resistance to shape change) in earlier Sn-VO_2 composites (*15*) that exhibited large damping but modest (5%) anomalies in the modulus. These three-dimensional aspects of deformation govern the stability and properties of materials. Positive values of G and K give rise to a positive-definite strain energy and hence to the stability of an object with free surfaces and no constraint. This corresponds to the usual allowable range of Poisson's ratio ν, $-1 < \nu < 0.5$, allowing a negative Poisson's ratio in isotropic solids (*5*). For the less restrictive condition of strong ellipticity, which entails real positive velocities of shear and longitudinal waves, $G > 0$ and $-4G/3 < K < \infty$. A strongly elliptic solid constrained at the surface is incrementally stable (*22*) and has a unique elasticity solution (*23*), so a range of negative bulk modulus is allowed. A material with negative shear modulus G is unstable with respect to domain formation. Surface energy limits how small a domain can be, so a sufficiently small crystal can be a single domain and can operate as a negative-stiffness inclusion, as was the case in Sn-VO_2 composites. There is no such inclusion size limitation associated with a negative bulk modulus. An inclusion in a composite is under partial constraint.

Diamond has long been considered to have maximal properties such as stiffness and hardness. The achievement of substantially greater stiffness illustrates the importance of composites with negative-stiffness inclusions. These composites have potential in high-performance materials in which high stiffness or high dissipation are of use. They may occur naturally in rocks and play a role in deep-focus earthquakes.

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Coupling Coherence Distinguishes Structure Sensitivity in Protein Electron Transfer

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Quantum mechanical analysis of electron tunneling in nine thermally fluctuating cytochrome b_{562} derivatives reveals two distinct protein-mediated coupling limits. A structure-insensitive regime arises for redox partners coupled through dynamically averaged multiple-coupling pathways (in seven of the nine derivatives) where heme-edge coupling leads to the multiple-pathway regime. A structure-dependent limit governs redox partners coupled through a dominant pathway (in two of the nine derivatives) where axial-ligand coupling generates the single-pathway limit and slower rates. This two-regime paradigm provides a unified description of electron transfer rates in 26 ruthenium-modified heme and blue-copper proteins, as well as in numerous photosynthetic proteins.

Many biological pathways depend on the facilitation of electron transfer (ET) processes by proteins (*1*–*14*). At the simplest level, this acceleration in rate can be explained by empirical models that omit the details of protein structure and describe the fact that proteins lower the barrier to electron tunneling by about 3 eV relative to that of vacuum tunneling (*1*, *14*). However, ET rates can be slower or faster in different proteins, despite the electron's traveling a similar distance between donors and acceptors (R_{DA}) (*1*–*3*). These rate differences can arise because tunneling is faster through covalent bonds than through weak or nonbonded contacts (*10*), and the composition of the coupling medium between donor and acceptor varies with the primary, secondary, and tertiary structure of the protein (*1*, *2*, *10*).

The simplest model that accounts for such structural effects on ET rates is the pathway model (*10*), which identifies the most facile coupling routes between the donor and acceptor. Packing-density models analyze atom density between the donor and acceptor. The predictions of the pathway and packing-density models are nearly the same (*4*, *15*). Nonetheless, there are many examples where an even simpler exponential model (*14*)

$$k_{ET} \propto \exp[-\beta R_{DA}] \qquad (1)$$

, where k_{ET} is the ET rate and β is an exponential decay constant, can account for the observed ET rates without including three-dimensional details of protein structure.

The limits of validity for these simple tunneling models have been poorly understood, and understanding has been further hampered by the lack of sufficiently detailed data sets on ET rates for the same protein that would allow for meaningful comparisons; in comparing ET rates between different proteins, it is difficult to separate the electron-tunneling factors from the nuclear factors, or Marcus factors (*16*), that arise in the ET theory (*1*, *2*). We have now analyzed a recent set of tunneling-limited ET rates obtained by Winkler and Gray for a Ru-modified heme protein [cytochrome (cyt) b_{562}]. The exponential distance-decay model accounts for some but not

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all of the observed rate dependences (*17*, *18*). We provide an explanation for the different rate behaviors in this protein, which can also account for ET kinetic data in other Ru-modified heme proteins (including cyt c and myoglobin).

Here, we argue that some protein structures generate exponential decay of coupling with distance (as if the proteins were structureless tunneling barriers) by dynamically averaging multiple-coupling pathways. Other protein structures, in contrast, retain pathway-specific coupling characteristics that may be very different from the "average" protein coupling for that R_{DA} value. We explain why the protein-mediated coupling falls either in the pathway or average-barrier regime, and we also find that a simple metric—the coupling coherence parameter (*19*)—provides a reliable indicator of the coupling mechanism. We restrict our discussion to unimolecular ET between sites within a protein, although interprotein ET appears to be even more sensitive to structure than unimolecular ET (*11*, *12*).

We briefly review the two structured-protein models (*1*, *10*). The pathway model predicts

$$k_{ET} \propto \left\{ \prod_i \varepsilon_i^{bond} \prod_j \varepsilon_j^{bond} \exp[-\beta^{space}(r_j - r_0)/2] \right\}^2 \quad (2)$$

where Π represents a product, ε^{bond} ~0.6 and β^{space} ~1 Å^{-1} are decay parameters associated with the dominant-coupling route from donor to acceptor through a combination of bonded and nonbonded contacts, r_j is the length of each through-space contact, and r_0 is 1.4 Å. The pathway-based rate is well approximated by means of an atomic packing-density model (*4*, *15*)

$$k_{ET} \propto \exp[-\beta^{space} f^{space} R_{DA}] \times \exp[-\beta^{bond}(1 - f^{space}) R_{DA}] \quad (3)$$

where the β parameters describe tunneling decay through bond or space, and $1 - f^{space}$ is the fraction of space between the donor and acceptor that is filled with atoms (*4*). The pathway and packing-density rates (Eqs. 2 and 3) include explicit information about the protein fold that is not included in the simple exponential model (square-barrier tunneling model), which uses a single fitted β value. Fully quantum treatments sum together contributions to the tunneling rate that arise from the multiplicity of donor-acceptor (D-A) pathways that couple donor to acceptor (*1*, *2*). In conformationally flexible systems, the mean square (ensemble-averaged) D-A coupling $\langle H_{DA}^2 \rangle$ determines the rate (*20*–*22*)

$$k_{ET} \propto \langle H_{DA}^2 \rangle \quad (4)$$

Here, we examine the tunneling-limited ET kinetics for Ru-modified cyt b_{562} (Fig. 1A) (*18*); each derivative explores the tunneling-mediation characteristics of a distinct protein region. All but two of these rates fit a simple square-barrier tunneling model (Fig. 1B). Two rates fall two orders of magnitude below the square-barrier (exponential distance-decay) model for tunneling in this protein. The ET kinetics in cyt b_{562} mirrors previous observations in Ru-modified cyt c [one of eight tunneling-limited rates is two orders of magnitude below an exponential fit (*17*)] and in myoglobin [one of three tunneling-limited rates is orders of magnitude slower than expected based on distance analysis (*17*)]. Cyt c data appear in fig. S1.

We first used a previously developed ab initio Hartree-Fock method to compute ET rates in these

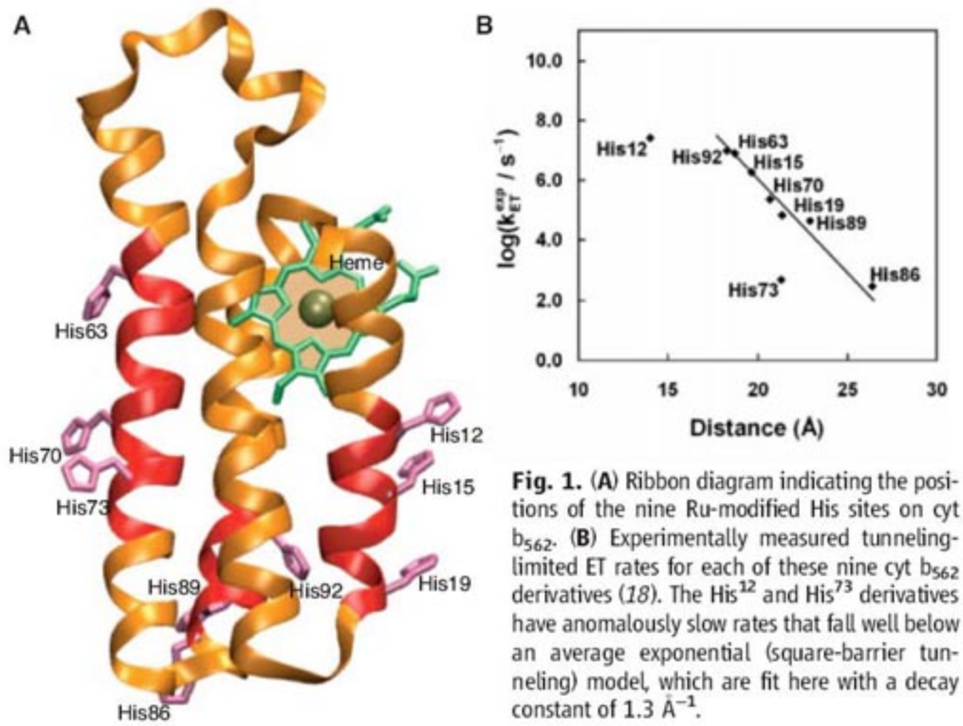

Fig. 1. (**A**) Ribbon diagram indicating the positions of the nine Ru-modified His sites on cyt b_{562}. (**B**) Experimentally measured tunneling-limited ET rates for each of these nine cyt b_{562} derivatives (*18*). The His^{12} and His^{73} derivatives have anomalously slow rates that fall well below an average exponential (square-barrier tunneling) model, which are fit here with a decay constant of 1.3 Å^{-1}.

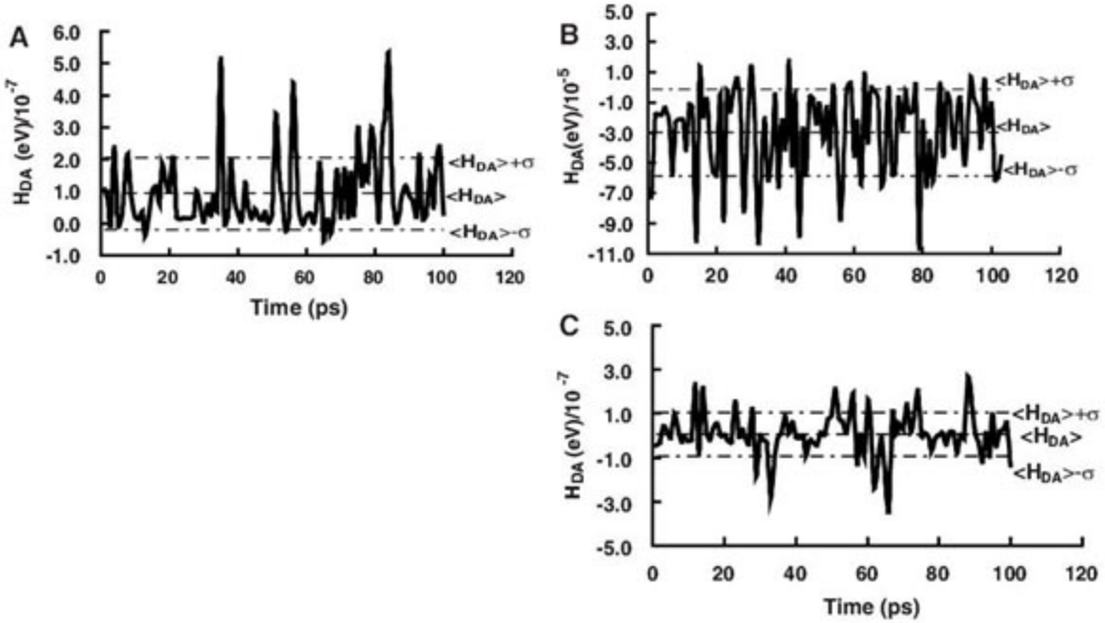

Fig. 2. Electronic couplings versus time. (**A**) His^{73} (C = 0.5), dominant-coupling pathway regime; (**B**) His^{12} (C = 0.6), dominant-coupling pathway regime; (**C**) His^{70} ($C = 4 \times 10^{-3}$), multiple-pathway mechanism. Note the frequent sign flips in (C), which are consistent with a multiple-pathway mechanism. In (A) and (B), $\langle H_{DA} \rangle^2$ differs by only about a factor of two from $\langle H_{DA}^2 \rangle$. Geometry snapshots were captured each 1 ps and input to the extended-Hückel coupling calculations.

cyt b_{562} systems (*23*, *24*). The correlation between computed and observed ET rates appears in fig. S2. Except for the longest-distance derivative (His^{86}), the measured and computed rates agree within a factor of four. This order of magnitude agreement, including a satisfactory description of the anomalously slow ET kinetics in the His^{12} and His^{73} derivatives, indicates that theory describes the essential aspects of ET kinetics in these complex systems. The computations include protein conformational averaging, solvation, and averaging of couplings over multiple ligand-field states with the use of methods described previously (*23*). The calculations explicitly include multiple-pathway interferences, without making empirical assumptions that are associated with dominant pathways or packing density.

We now examine the physical origin of the two slow ET rates, as well as the simple (exponential) distance dependence for the other seven derivatives. To perform this analysis, we computed D-A interactions for protein structure shapshots taken from classical molecular dynamics (MD) trajectories. Because the number of calculations needed for this analysis is large, we used an extended-Hückel Hamiltonian. Extended-Hückel analysis of D-A interactions in proteins has been used successfully in previous studies of Stuchebrukhov and Marcus (*25*), Kakitani (*26*), Onuchic (*6*), and others. Our analysis assumes metal-localized states to describe the $Fe^{2+} \rightarrow Ru^{3+}$ ET (*17*).

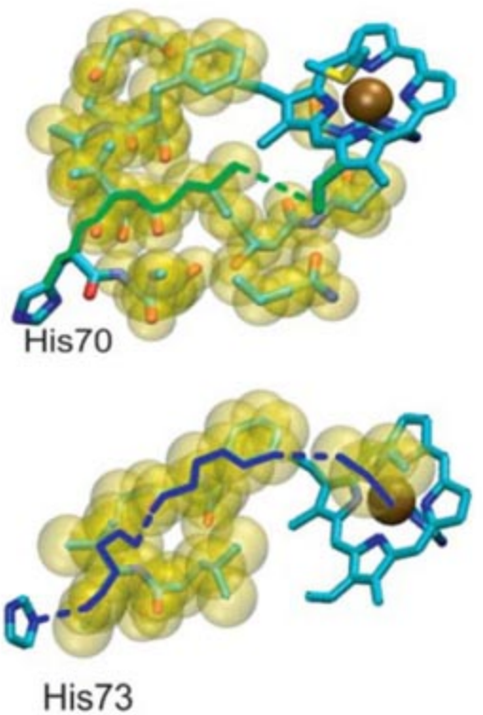

Fig. 3. Pruned protein media [5% cutoff criterion (*23*)] for His^{70} (average-medium or multiple-pathway regime, small *C* parameter) and His^{73} (single-pathway regime, large *C* parameter). Both proteins have ET distances of ~20 Å metal-to-metal. The strongest single pathways are noted with solid and dashed lines. Spheres are shown on atoms included in the quantum tunneling analysis (*23*).

The string of computed coupling interactions allows us to calculate the Balabin-Onuchic coherence parameter, $C = \langle H_{DA} \rangle^2 / \langle H_{DA}^2 \rangle$ (*19*), for the ruthenated proteins. We expect *C* to be very small when numerous interfering coupling pathways contribute to the D-A interaction. In this limit, only average characteristics of the protein fold determine the ET rate. In contrast, when *C* is near unity, a dominant-coupling pathway mediates tunneling, and the observed rate is characteristic only of that pathway's structure. Indeed, the His^{12} and His^{73} derivatives of cyt b_{562} have *C* parameters of 0.6 and 0.5, respectively, whereas all other derivatives have *C* values of 0.1 or less (table S2).

Coupling values along 100-ps MD trajectories for His^{12}, His^{70}, and His^{73} appear in Fig. 2. The coupling values along the MD trajectory for the His^{73} ($C = 0.5$) and His^{12} ($C = 0.6$) derivatives rarely change sign (Fig. 2, A and B), which is characteristic of the dominant pathway regime. The His^{70} derivative [$C = 4 \times 10^{-3}$] has a coupling value that fluctuates about zero and a mean coupling value squared ($\langle H_{DA} \rangle^2$) that is orders of magnitude smaller than the mean squared coupling value ($\langle H_{DA}^2 \rangle$). This small *C* regime is characteristic of multiple interfering coupling pathways of comparable strength, so the $\langle H_{DA}^2 \rangle$ value is averaged over many pathways and is characteristic of the overall protein fold rather than of a single dominant-coupling pathway. In contrast, coupling in the large *C* regime is determined by the structure of the dominant-coupling pathway.

What aspects of structure in a single protein can generate this substantial difference in mechanism? Simple tunneling-pathway analysis of the cyt b_{562} His^{12} and His^{73} derivatives provides the answer. The two large *C*-parameter (dominant pathway) structures have coupling pathways linked to the heme through an axial ligand, but seven other derivatives each have surface Ru complexes that are coupled electronically by multiple pathways to the heme edge. The tunneling-pathway analysis (fig. S3) reveals this aspect of protein connectivity.

Because of the large size of the heme-edge "target," coupling into the heme edge in cyt b_{562} generates multiple interfering pathways with mean squared values that reflect average coupling characteristics of the many pathways. The axial-ligand pathway derivatives, in contrast, have a smaller number of sizable coupling pathways leading to the heme (Fig. 3), because coupling routes must proceed through one single metal-ligand pathway bottleneck. In cyt b_{562}, this connectivity gives rise to single-pathway (large *C* value) mechanisms. Moveover, the axial ligand's van der Waals volume apparently serves to minimize the presence of multiple coupling routes to the prophyrin ring face. This contrasts with the large circumference heme-edge access provided by noncovalent interactions. In the case of cyt b_{562} (and for other Ru proteins, as described below), pure axial pathways have large *C* values (i.e., dominant pathways), are poorly "wired" to the heme, and produce slow tunneling-limited rates. It appears that dynamical averaging over many coupling pathways operates in cyt b_{562} for all heme-edge–coupled derivatives, producing simple (exponential) decay with distance as described by Eq. 1.

Is the observation of weak single-pathway (large *C*) axial coupling and strong multiple-pathway heme-edge coupling (small *C*) in cyt b_{562} relevant to other Ru-modified heme proteins and to native proteins? The one anomalously slow ET derivative in the Ru–cyt c family is the His^{72} derivative (fig. S1) (*17*), and the dominant-coupling pathway to the heme is routed via an axial ligand. The anomalously slow His^{83} derivative of the Ru-myoglobin family is also dominated by an axial-ligand pathway. All "average" rates in cyt c and myoglobin (i.e., those rates that fit well by a single exponential decay law) access multiple-coupling pathways, including heme-edge–coupled pathways. As such, our distinction between multiple-pathway heme-edge–coupling routes and axial-ligand–dominated single-coupling routes rationalizes all of the anomalously slow ET rate data among 20 ground-state Ru-modified heme proteins (*3*, *17*).

Our heme-protein analysis indicates that exponential distance dependence for protein ET rates occurs in the small *C* multiple-pathway regime. Because small *C* values have been computed in nonheme proteins as well, we can further explore the correlation between small *C* values and exponential distance decay. Previous theoretical analysis of the blue-copper protein azurin indicates that all six Ru derivatives have very small *C* values (*27*), which is consistent with the measured single exponential decay of rates with distance in this protein for all derivatives (*17*). In azurin, the three strong coupling routes to the copper or the pathway cross-linking by hydrogen bonds provide likely physical sources of average-medium behavior. Although coherence parameter analysis remains to be performed for the Ru-modified high-potential iron protein (*28*), we expect that the anomalously slow Ru-His^{50} derivative will also have a large *C* associated with a weak dominant-coupling pathway. Rates in all 26 ruthenated myoglobin, cyt c, cyt b_{562}, and azurin derivatives are explained within the dichotomy of an average-medium tunneling (small *C*) model or a single-pathway tunneling (large *C*) model. In Ru-modified heme proteins, heme-edge coupling produces average-medium behavior, whereas axial-ligand coupling generates pathway-specific D-A interactions.

Tunneling-limited ET rates in the photosynthetic reaction center (PRC) follow an exponential distance-decay law (*4*). Preliminary analysis of coherence parameters in the PRC charge transfer reactions indicates values of 10^{-2} or less, which are consistent with multiple edge-coupled pathways and average-medium behavior. We find similar behavior in the DNA repair protein photolyase, where ET couples two delocalized pi-electron states (*29*).

The accessibility of two coupling mechanisms seems essential for the analysis of evolutionary pressure on ET proteins. Earlier arguments

regarding pathway evolution had been made along two lines. Simple (exponential) distance dependencies observed in the photosynthetic proteins led Moser, Dutton, and co-workers to suggest that evolution manipulates ET rates using R_{DA} and Marcus (nuclear) parameters (*4*). Gray, Winkler, and co-workers, in contrast, argued that strong pathways have evolved to accelerate ET in some proteins (*5*). Indeed, the structure of common biological redox cofactors seems to permit ET proteins to access both mediation regimes.

We suggest that, in the multiple-pathway regime, the evolutionary linkage between the specific protein fold and the ET rate is likely to be weak: In this regime, R_{DA} determines tunneling propensity. In the single-pathway large C regime, however, ET kinetics and protein structure are strongly linked. Although the Ru proteins only display slow rates in the dominant pathway regime, either strong or weak coupling pathways could arise in the dominant pathway regime, generating order of magnitude effects on the ET kinetics from protein structure. This structure-function perspective extends the pathway-evolution conjecture of Ramirez *et al*. (*5*), by accounting for the influence of thermal motion on the protein-mediated coupling, and also suggests that the Moser-Dutton (average-medium) view is valid in the multiple-pathway regime common to many large edge-coupled redox cofactors. Tunneling routes involving axial ligands seem to be the most likely candidates for kinetics that is sensitive to coupling pathway structure [e.g., the heme a to heme a_3 pathways in cyt c oxidase (*5*, *6*)]. How often and where nature has used pathway-specific or multiple-pathway regimes remain to be determined by future analysis and experiments. Also, in the small C regime, proteins will have ET kinetics that are robust to modifications of single-pathway links (e.g., by manipulating hydrogen bonding), whereas pathway structural changes in the large C regime may have a larger influence on ET kinetics (*30*–*32*).

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Supporting Online Material

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Figs. S1 to S3
Tables S1 and S2

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Thymine Dimerization in DNA Is an Ultrafast Photoreaction

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Femtosecond time-resolved infrared spectroscopy was used to study the formation of cyclobutane dimers in the all-thymine oligodeoxynucleotide $(dT)_{18}$ by ultraviolet light at 272 nanometers. The appearance of marker bands in the time-resolved spectra indicates that the dimers are fully formed ~1 picosecond after ultraviolet excitation. The ultrafast appearance of this mutagenic photolesion points to an excited-state reaction that is approximately barrierless for bases that are properly oriented at the instant of light absorption. The low quantum yield of this photoreaction is proposed to result from infrequent conformational states in the unexcited polymer, revealing a strong link between conformation before light absorption and photodamage.

The most abundant lesion in ultraviolet (UV)–irradiated DNA is the cyclobutane pyrimidine dimer (CPD) that is formed between adjacent thymine bases (Fig. 1) (*1*). This mutagenic photoproduct disrupts the normal cellular processing of DNA and leads to a complex web of biological responses, including apoptosis, immune suppression, and carcinogenesis (*2*–*4*). Organisms possess elaborate repair pathways to counter this constant threat to genomic integrity. Aside from their biological importance, CPDs are of interest as structural reporters. Thymine-dimer yields are not the same at all TT doublets in a given DNA sequence, but these yields depend, in poorly understood ways, on the identity of the flanking bases and on local conformation (*1*). By exposing DNA to UV light and then measuring the relative photoproduct yields with single-nucleotide resolution, it has been possible in favorable cases to obtain structural information (*5*–*7*). In order for this methodology to achieve its full potential, molecular-level understanding of the dimerization mechanism is essential. We report a dynamic study of thymine dimerization that provides insight into the coupling between DNA structure and DNA photodamage.

CPD formation is a [2+2] photocycloaddition reaction in which the carbon-carbon double bonds of proximal pyrimidine bases react to form a cyclobutane ring. In the analogous reaction between two ethylene molecules, electronic excitation and the proper orientation of the reacting double bonds are needed for the reaction to occur (*8*). Unlike the case of free ethylene molecules, pyrimidine bases in DNA are tethered to the sugar-phosphate backbone, and this tethering restricts the achievable orienta-

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tions. Some conformations are simply impossible because of backbone constraints. Thus, a single CPD isomer (the cis-syn isomer shown in Fig. 1) is formed in UV-irradiated oligo- and polynucleotides, whereas two thymine molecules diffusing freely in aqueous solution yield all six stereoisomers (*1*). Because DNA is moderately flexible, a vast number of conformations exist. Some of these have the bases positioned favorably for a reaction, whereas others do not. DNA is highly dynamic, and motions such as the stacking and unstacking of bases, base-pair breathing and opening, torsional oscillations, and helix bending will incessantly bring a given bipyrimidine doublet into and out of favorable geometries for dimerization. The impact of these motions on the reaction kinetics depends on how their rates compare to the rate of reaction by favorably oriented bases (*9*). Direct kinetic measurements of dimerization can thus elucidate the potentially complex interactions between conformational dynamics and photodamage.

In an excited-state reaction, motion along the reaction coordinate occurs in competition with energy-wasting steps such as fluorescence and internal conversion to the electronic ground state. In the past few years, it has become possible to directly observe the dynamics of excited electronic states in DNA model compounds by femtosecond spectroscopy (*10*, *11*). It has been proposed that the very high rate of nonradiative decay by the singlet $\pi\pi^*$ ($^1\pi\pi^*$) states of single nucleobases can greatly restrict photodamage (*10*). However, recent work has revealed the presence of additional, rather long-lived singlet states in DNA (*11*) and single bases (*12*). In oligodeoxynucleotides, lifetimes of <1 ps to >100 ps have been observed, depending on base stacking and base sequence (*11*). Additionally, at least 10% of all singlet excitations in single pyrimidine bases such as thymidine 5′-monophosphate (TMP) decay to singlet $n\pi^*$ ($^1n\pi^*$) excited states with lifetimes in excess of 10 ps (*11*). Kinetic measurements can determine which of these diverse excited states is the dimer precursor.

Past efforts to observe dimerization kinetics have been unsuccessful. It has been shown by flash photolysis that photodimers are formed in the all-thymine oligodeoxynucleotide $(dT)_{20}$ in <200 ns, the time resolution of the laser system that was used (*13*). Femtosecond transient electronic spectroscopy (*11*) has not provided direct evidence for dimer formation because CPDs do not absorb at wavelengths longer than ~270 nm. Because of its chemical bond specificity, vibrational spectroscopy can often unambiguously identify transient species and stable photoproducts (*14*). We therefore recorded time-resolved infrared spectra of a DNA model compound that was excited by a femtosecond UV pump pulse (*15*). The system studied was single-stranded $(dT)_{18}$, which was chosen in order to maximize the number of dimers that were formed with each laser pulse. In this DNA model system, every absorbed photon excites a residue that is capable of dimerization. Quantum yields in the closely related systems poly(dT) (0.033) (*16*) and $(dT)_{20}$ (0.028) (*13*) are among the highest reported for any DNA compound. In contrast, the dimerization quantum yield is over 30 times lower in double-stranded genomic DNA (*17*). This large reduction is due to the low frequency of TT doublets and the absorption by nonthymine bases in mixed-sequence DNA. After presenting our results for $(dT)_{18}$, we will discuss the implications for double-stranded nucleic acids.

Steady-state infrared (IR) absorption spectra of $(dT)_{18}$ in D_2O were recorded before and after UV irradiation at 266 nm, in order to locate IR marker bands that were indicative of dimerization. In the spectrum obtained before UV irradiation (black curve in Fig. 2A), three strong bands were observed at 1632, 1664, and 1693 cm^{-1}. These bands, which arise from double-bond stretches associated with the two carbonyl groups and the C5=C6 double bond (*18*), bleached strongly after several minutes of UV exposure (Fig. 2A). Difference spectra were calculated by subtracting the steady-state IR spectrum from each spectrum of the UV-irradiated oligomer (Fig. 2B). Negative bleaching signals were apparent in the double-bond stretching region above 1600 cm^{-1}. In addition, positive peaks between 1300 and 1500 cm^{-1} grew in with increasing exposure time. The IR absorption spectrum of the photoproduct (solid curve, Fig. 2C) was obtained from the difference spectra in Fig. 2B by target analysis (*19*), assuming that a single photoproduct is formed. In fact, a pyrimidine (6-4) pyrimidone photoadduct is also generated at TT doublets, but it

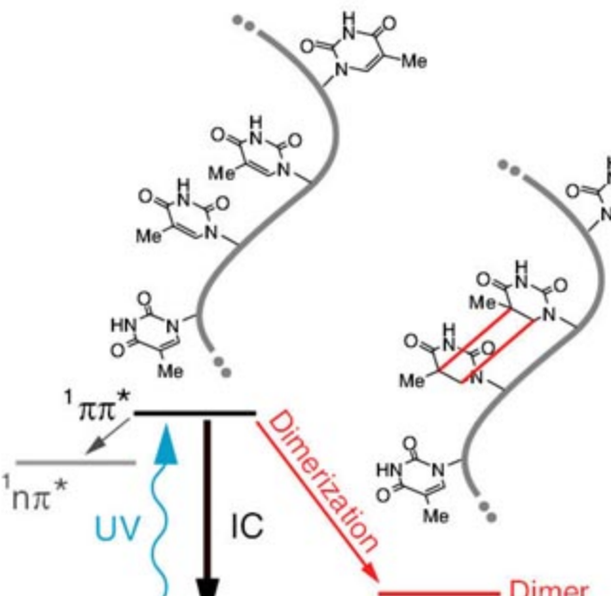

Fig. 1. Schematic of the photodynamics of the DNA oligomer $(dT)_{18}$. The DNA's sugar-phosphate backbone is shown as a gray ribbon in the partial structures. UV excitation populates a singlet $\pi\pi^*$ state. This state decays overwhelmingly via internal conversion (IC) to the S_0 ground state. To a smaller extent, the population of the $\pi\pi^*$ state branches to a singlet $n\pi^*$ state. Intersystem crossing to a triplet state has been detected in thymine but not in polymeric DNA. Finally, the $\pi\pi^*$ state can decay to a dimer photoproduct (middle residues with new bonds shown in red) if a reactive conformation is present at the time of excitation.

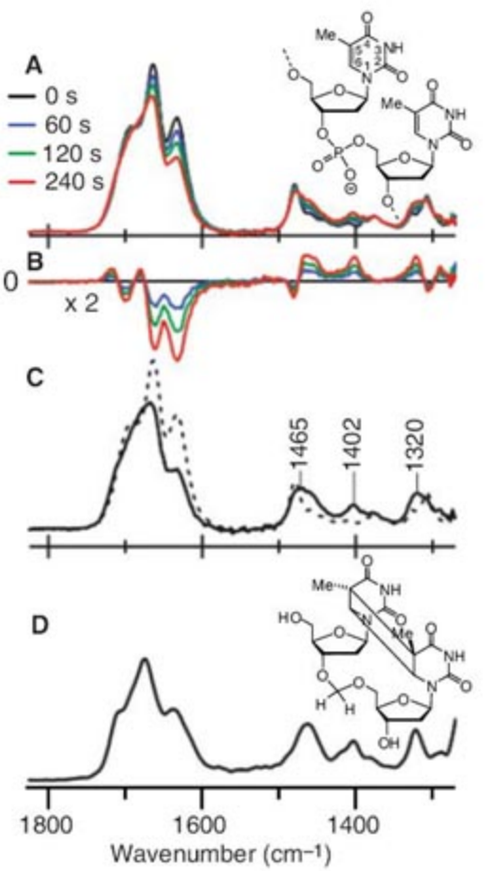

Fig. 2. (**A**) IR absorption spectra of $(dT)_{18}$ (partial structure shown at right; Me, methyl) in D_2O after exposure to UV laser pulses at 266 nm for the times indicated. (**B**) Difference IR spectra from the data in (A). (**C**) IR absorption spectrum of the photoproduct obtained from the data in (B) by target analysis (solid curve), showing three distinctive marker bands between 1300 and 1500 cm^{-1}. The IR absorption spectrum of $(dT)_{18}$ before UV irradiation is shown for comparison (dashed curve). (**D**) Steady-state IR absorption spectrum of the cis-syn dimer model compound in D_2O (structure shown at right).

can be neglected because its quantum yield is 50 times lower in poly(dT) (*20*). The absorption spectrum (Fig. 2D) of a previously described model compound of the cis-syn thymine dimer (*21*) is in excellent agreement with the solid trace in Fig. 2C, showing that this is the only dominant photoproduct under these conditions. Bands in the dimer spectrum substantially overlap those of unirradiated $(dT)_{18}$ above 1500 cm^{-1}. In contrast, a trio of marker bands is evident at 1320, 1402, and 1465 cm^{-1} (Fig. 2C), and these bands became the focus of the time-resolved experiments.

Broadband IR transient absorption signals were recorded between 1300 and 1550 cm^{-1} after excitation of $(dT)_{18}$ by a femtosecond pump pulse at 272 nm (*15*). For comparison, measurements were carried out on TMP, which cannot dimerize on the time scales of interest here because of the slow rate of diffusional encounter by two TMP molecules. Transient spectra measured for both solutes are compared side-by-side in Fig. 3. Negative absorbance changes (bleaches) are colored blue, whereas positive signals are red. The bleaches monitor the repopulation of the starting material, whereas positive signals arise from the vibrational bands of excited states or photoproducts. At first glance, the transient IR spectra of TMP and $(dT)_{18}$ are very similar. The quantum yield for dimerization in $(dT)_{18}$ is just 2 to 3%, and most excitations in both systems decay nonradiatively on similar time scales (*11*).

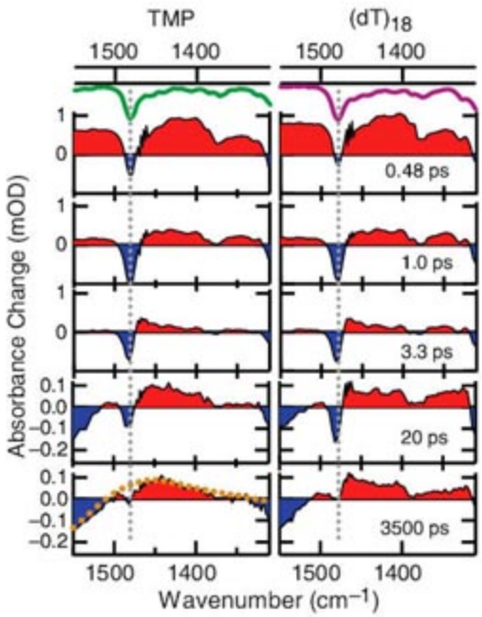

Fig. 3. Transient IR difference spectra at the indicated times after 272-nm excitation of TMP and $(dT)_{18}$ in D_2O solution in the photodimer marker-band region (typical errors are ~10 μOD). Positive bands are shaded red, whereas negative signals are shaded blue. The green and purple curves at the top show the inverted steady-state IR spectra of each solute. Strong bands are indicated by the vertical dashed gray lines. The yellow dashed curve in the 3500-ps spectrum of TMP represents the steady-state difference IR spectrum obtained by raising the temperature of neat D_2O (see SOM). After ultrafast internal conversion of the excited molecules, the transient spectra are dominated by the cooling dynamics of the hot ground states on a time scale of several picoseconds. Transient spectra at later delay times show the broad signature of the heated solvent. The residual bleach seen for TMP at 3 ns is assigned mainly to intersystem crossing to a triplet state [estimated quantum yield ≤0.02 (*1*)]. For $(dT)_{18}$, one can see additional absorption due to the presence of thymine dimers.

Dynamic events revealed by the time-resolved spectra in Fig. 3 that are common to both solutes are discussed first. Initially, UV excitation populates the lowest-energy $^1\pi\pi^*$ state, resulting in bleaches at frequencies corresponding to ground-state vibrations (dashed gray lines in Fig. 3). These bleaches have their maximum amplitudes near time zero, as seen in the spectra recorded 0.48 ps after the pump pulse. Positive signals are seen at this time at all frequencies where bleaching is not observed. These broad bands decay with a lifetime close to that of the $^1\pi\pi^*$ state [540 fs for thymidine (*10*)] and are no longer present in the 3.3-ps spectra. The short lifetime of this state is limited by internal conversion, which moves the population nonradiatively from the $^1\pi\pi^*$ state to the vibrationally excited electronic ground state. The photon energy is thus converted into sudden vibrational heating. This produces positive bands on the red edge of the negative bleach signals, resulting in distinctive sigmoidal line shapes (*22*) such as the one seen near 1480 cm^{-1} in the 3.3-ps spectra. These features disappear by vibrational energy transfer to the solvent (vibrational cooling), with a time constant of 2 to 4 ps (*11*, *14*), and are no longer visible at 20 ps.

The bleach near the maximum of each vibrational mode recovers in multiexponential fashion with similar kinetics as those that were previously recorded by transient absorption signals at UV wavelengths (*11*). The decay is 85 to 90% complete within 10 ps, whereas the remainder of the bleach recovers with time constants that vary between 100 and 1000 ps because of the decay of the $^1n\pi^*$ population (*12*). A broad positive band near 1350 cm^{-1} decays on a 100-ps time scale and is tentatively assigned to this $^1n\pi^*$ state. The spectra at 3 ns (Fig. 3) are dominated by a broad sigmoidal line shape, extending from 1300 to 1800 cm^{-1}. This distinctive signature arises from a temperature-jump effect, which is described in the supporting online material (SOM) in more detail. The hot-water contribution to the transient spectrum appears within a few picoseconds, but it then remains constant in our time window because of slow heat transport out of the laser focus (*23*).

There are subtle but significant differences between the time-resolved IR spectra in Fig. 3. Greater modulation in the 20-ps and 3.5-ns spectra for $(dT)_{18}$ is due to absorption in the oligomer at each of the three marker-band frequencies that are identified in Fig. 2C. The difference is readily seen in a comparison of the transient spectra that are recorded for the two samples at a 3-ns delay time in the top panel of Fig. 4A. The water-heating signal is approximately the same for both samples because of the similar extent of ultrafast nonradiative decay. This signal can therefore be removed by subtracting the transient spectrum for TMP from the spectrum that was recorded at the same delay time for $(dT)_{18}$. Difference spectra constructed in this manner are shown by the blue curves in Fig. 4A and as a contour plot between 1 and 25 ps in Fig. 4B. The subtraction procedure is discussed at length in the SOM.

The red trace in Fig. 4A is the difference spectrum calculated by subtracting the ground-state absorption spectrum of $(dT)_{18}$ from the dimer spectrum of Fig. 2C. This trace represents the expected absorption changes induced by dimer formation. The transient difference spectra at 15 ps and 3 ns show positive peaks at each of the dimer marker-band frequencies and contributions from ground-state bleaching. The excellent agreement with the stationary spectrum shows unequivocally that thymine dimers are present ~15 ps after excitation.

The dynamics of the marker bands at earlier times can be seen in a contour plot of the transient difference spectrum between 1 and 25 ps (Fig. 4B). The positive marker bands at 1402 and 1320 cm^{-1} are clearly visible over the entire time range. The marker band at 1465 cm^{-1} is visible down to 4 ps, but it is obscured by vibrational cooling of hot thymine molecules at earlier delay times. Because TMP and $(dT)_{18}$ exhibit different cooling dynamics (*11*), the vibrational cooling signatures do not fully cancel each other and instead show up in the difference plot in the vicinity of intense ground-state bands. Thus, the cooling dynamics from the hot 1480 cm^{-1} band (Fig. 3) cover the 1465 cm^{-1} marker band at early delay times. Cooling is also seen at other wavenumbers during the first few picoseconds; e.g., around 1350 cm^{-1}. For delay times <1 ps, the signals are dominated by ultrafast relaxation of the electronically excited state, which obscures direct observation of dimer formation at the shortest times. Nevertheless, the observation of the dimer marker bands 1 ps after light absorption indicates that the reaction occurs on a femtosecond time scale.

The dimer yield can be estimated from the average amplitude of the marker bands in Fig. 4 of ~30 μ–optical density (OD) units. This is 3% of the initial bleach of 1 mOD that was seen 1 ps after photoexcitation at 1480 cm^{-1}. This band has a cross section comparable to that of the three marker bands, so the reported dimerization yield of 2 to 3% (*13*, *24*) should produce a signal of 20 to 30 μOD, as observed. The dimer yield at ~1 ps thus equals the value from steady-state experiments within experimental uncertainty, demonstrating that dimerization is

an ultrafast photoreaction. The high speed of this bond-forming reaction is noteworthy but not unprecedented. Ultrafast reaction rates are seen for some bimolecular reactions when the reactants are suitably preoriented (*25*). Also, the closely related intramolecular [2+2] photocycloaddition reaction of norbomadiene occurs in the gas phase in <100 fs (*26*).

The ultrafast time scale of thymine dimerization suggests that an essentially barrierless path connects the initial $^1\pi\pi^*$ state with the end product. This suggests that a conical intersection lies along this path as in computational studies of other pericyclic photoreactions (*8*). Dimerization in $(dT)_{18}$ occurs more rapidly than many motions that could bring poorly oriented bases into a more favorable conformation for reaction. For example, base stacking and unstacking in thymine oligomers require tens of picoseconds, according to a molecular-dynamics study (*27*). Dimerization thus occurs only for thymine residues that are already in a reactive conformation at the instant of excitation (*28*, *29*). Excited states of unfavorably oriented thymines are quenched before a change of conformation can occur. The extent of dimerization under steady-state irradiation thus depends on the fraction of time that a given doublet spends in reactive versus nonreactive conformations. Control of CPD formation by ground-state structure is fully consistent with the rapid saturation of CPD formation in poly(U) and poly(dT) in a rigid glass at 77 K as compared to room-temperature aqueous solution (*30*). This occurs because there is a finite number of reactive conformations in the low-temperature polymer, but the polymer in room-temperature solution is able to thermally fluctuate, allowing new reactive conformations to appear as exposure continues.

Because the rate of reaction by favorably aligned thymines is much faster than the rate of conformational change, the quantum yield is equal to the fraction of reactive conformations multiplied by the probability that a reactive conformation dimerizes upon excitation (*9*). The latter quantity is unknown, but it is likely to approach unity based on the high quantum yields of dimerization in molecular crystals of some pyrimidine bases (*31*) and in dimers split in rigid matrices (*32*). With this assumption, the quantum yield for dimerization is simply the fraction of favorably oriented conformations. The low yields for all-thymine oligomers thus reveal that only a few percent of the TT doublets are favorably positioned for reaction at the time of excitation. This finding is consistent with the disordered structure of this rather flexible oligomer (*33*).

Excited-state modeling is needed to fully characterize the reactive conformations, but some geometrical requirements are readily anticipated. Base stacking, which has been discussed in the past as a necessary criterion for reaction (*30*), reduces the distance between C5=C6 bonds as compared to an unstacked geometry. However, the dimer geometry suggests that a low value of the dihedral angle between the reacting double bonds may also be important. The conformational changes, such as partial helix unwinding and bending (*34*), that are observed near the site of a CPD are likely to be the same ones needed to make a conformation favorable for reaction (*7*).

We fully expect thymine dimerization to be ultrafast in double-stranded DNA, based on the speed of the reaction in single-stranded $(dT)_{18}$. Base pairing could affect the rates of nonreactive decay steps such as internal conversion by the precursor excited state, but we consider this to be unlikely, because recent time-resolved measurements show no effects due to base pairing on the dynamics of the excited states in AT-containing oligodeoxynucleotides (*11*). We conclude that dimerization occurs with equal speed for bipyrimidine doublets in single- and double-stranded contexts, provided that the TT geometry is similar for both contexts. Base pairing, on the other hand, will greatly influence the quantum yields by altering the distribution of conformations. The structures of flexible all-thymine oligomers (*27*, *33*) and double-stranded mixed-sequence DNA differ substantially, yet the quantum yields calculated per photon absorbed by a dimerizable thymine (see SOM) are the same to within a factor of ~2 in room-temperature aqueous solution (*17*, *35*). This means that a small percentage of TT doublets react in double-stranded DNA, even though virtually all doublets are well stacked. We propose that the winding of base pairs around the helix axis [the average twist angle is 36° in the B-type DNA (B-DNA) conformation (*36*)] keeps the C5=C6 double bonds too far apart. In contrast, although base stacking in single-stranded thymine oligomers is rare, the more flexible backbone does not prevent these rare stacks from adopting conformations that are suitable for dimerization.

A comparison of the literature that describes dimer yields in nucleic acids with A-type and B-type double-helical structures supports the hypothesis that dimerization in double-stranded DNA occurs as a result of uncommon conformations. The rate of dimer formation is decreased by up to a factor of 2 when double-stranded DNA is switched from the B-type to the A-type conformation (*37*). Even larger protective effects have been observed at TT steps in hairpins with A-type structure (*38*). The same base pairing is found in both structural classes, and the only difference is the distribution of accessible conformations. This evidence establishes that the conformation controls the reactivity in duplex DNA, just as in single-stranded $(dT)_{18}$. The average twist angle between successive base pairs differs in A-DNA by only a few degrees when compared to B-DNA, suggesting that the ideal geometries in both helices are nonreactive. Instead, dimerization is proposed to take place at TT steps that deviate in just the right way from the average duplex structure. Thus, the smaller amount of conformational variation in A-type versus B-type structures (*36*) explains the greater resistance of A-DNA to CPD formation.

The model we have derived from our results implies that static TT conformation (*7*, *29*), and

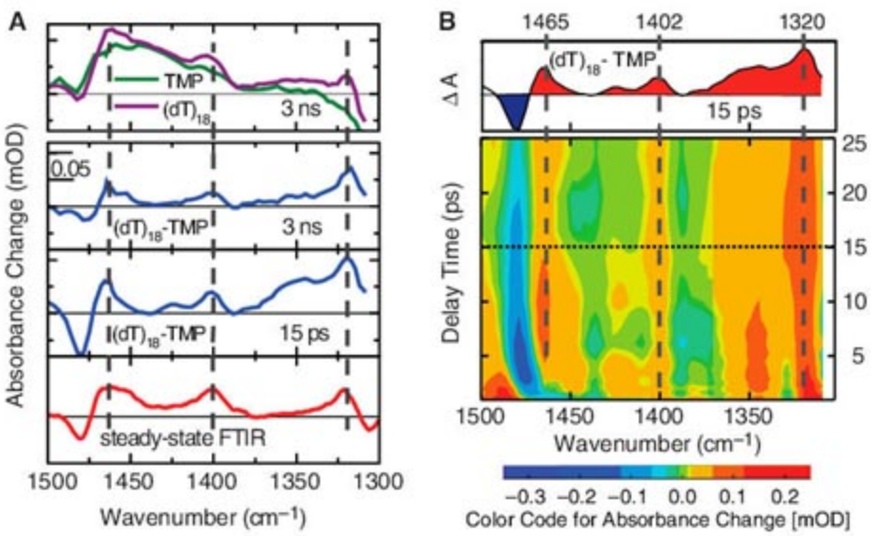

Fig. 4. Difference spectra formed by subtracting the transient spectra of TMP from those of $(dT)_{18}$. (**A**) The top panel shows the transient spectra of TMP and $(dT)_{18}$ at 3 ns. Their difference is plotted below as the blue curve, together with a difference spectrum at 15 ps. The red curve at the bottom represents the stationary IR difference spectrum of $(dT)_{18}$ (dashed curve in Fig. 2C) and the dimer photoproduct (solid curve in Fig. 2C). It displays the absorption difference due to dimer formation. Vertical dashed gray lines indicate the position of the cyclobutane dimer marker bands. (**B**) Contour plot of the difference spectrum. Red and blue colors represent strong positive and negative differences, respectively. A time slice showing the difference spectrum at 15 ps (horizontal dashed line in bottom panel) is shown in the top panel. Positive signals due to dimer formation are visible from ~1 ps onward for the bands at 1402 and 1320 cm^{-1}, as indicated by the vertical dashed lines. Because vibrational cooling dynamics differ for $(dT)_{18}$ and TMP, incomplete subtraction in the spectral region around the 1480 cm^{-1} ground-state band obscures the 1465 cm^{-1} photodimer band at early times.

not conformational motions after photoexcitation (*6*, *39*), determines the outcome of a reaction. Flexibility does not help an excitation at a bipyrimidine doublet attain a better conformation within its lifetime, but a more flexible backbone can increase the fraction of reactive conformations that are present at the time of light absorption. With knowledge about the conformational criteria that make reaction inevitable, molecular-dynamics simulation can be used to identify damage hot spots.

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Single Photon–Induced Symmetry Breaking of H_2 Dissociation

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H_2, the smallest and most abundant molecule in the universe, has a perfectly symmetric ground state. What does it take to break this symmetry? We found that the inversion symmetry can be broken by absorption of a linearly polarized photon, which itself has inversion symmetry. In particular, the emission of a photoelectron with subsequent dissociation of the remaining H_2^+ fragment shows no symmetry with respect to the ionic H^+ and neutral H atomic fragments. This lack of symmetry results from the entanglement between symmetric and antisymmetric H_2^+ states that is caused by autoionization. The mechanisms behind this symmetry breaking are general for all molecules.

Symmetries are essential building blocks of our physical, chemical, and biological models. For macroscopic objects, symmetries are always only approximate. By reducing the complexity in the microcosm, these symmetries often become strict. Thus, in any symmetric molecule, the ground state has a well-defined parity. This property has far-reaching consequences, such as truncation of rotational spectra or the existence of ortho- and para-molecular isomers (*1*). One way to break the symmetry is isotopic substitution of one of the nuclei (*2*). In larger systems, symmetry breaking can also be achieved through selected vibrational modes, such as asymmetric stretch, which lies at the origin of the Jahn-Teller and Rener-Teller effects (*3*). Alternatively, external fields can be used to favor a particular molecular direction, a method that has recently been used by Kling *et al.* (*4*) to induce asymmetric dissociation of the H_2^+ molecular ion into a proton and a hydrogen atom. Here, we show that, in dissociative ionization by absorption of a single photon

$$h\nu + H_2 \rightarrow p + H + e^- \qquad (1)$$

symmetry breaking is possible even in the absence of an external field. This is the smallest and most fundamental molecular system for which such symmetry breaking is possible.

Symmetry operations in a molecule that has a well-defined parity can change the sign of the ground state wave function (odd parity, or ungerade, states). However, all observables must be symmetric, because they are squares of wave functions or transition matrix elements. To achieve left-right asymmetry in an observable, the system must be put into a coherent superposition of gerade (g) (even) and ungerade (u) (odd) molecular states. The relative phase between the two states can then lead to a left or right localization of an electron. Direct photoionization usually cannot induce this outcome, because the g and u states of the remaining molecular ion have different energies. Therefore, two ionization pathways are distinguishable by the electron energy and hence the coherence is lost.

Figure 1A shows the energy diagram for the H_2 and H_2^+ molecules. The energy difference between the lowest g and u states in H_2^+, $^2\Sigma_g^+(1s\sigma_g)$ and $^2\Sigma_u^+(2p\sigma_u)$, respectively, is about 17 eV in the Franck-Condon region of H_2. Thus, if H_2 is directly ionized in a vertical transition by a photon of energy $h\nu$, the photoelectron will have an energy of about $E_e = h\nu - 16$ eV when the remaining H_2^+ is in the g state, whereas it will have $E_e = h\nu - 33$ eV when the remaining H_2^+ is in the repulsive u state. Both ionization paths are distinguishable by the energy (Fig. 1, B and C). Because in either path H_2^+ is in a state of well-defined parity, it manifests no memory of the direction toward

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which the photoelectron is emitted. We show that such a memory becomes possible if indirect pathways of ionization through doubly excited states are taken into account (Fig. 1, D and E).

The quantum dynamics of the population and decay of doubly excited states presents an important and fundamental challenge to theory. The full four-body problem must be treated entirely with quantum mechanics, without semiclassical approximations for the nuclear motion. Our ab initio calculation meets this challenge. In the accompanying kinematically complete experiment, we used cold target recoil ion momentum spectroscopy (COLTRIMS) (*5*, *6*) to provide the most detailed possible check of this theory. We calculated and measured the vector momenta of the proton and the ejected electron in coincidence. Because the dissociation is rapid compared with molecular rotation, the direction of fragmentation coincides with the molecular orientation at the instant of electron emission. Thus, measurements of the electron angular distribution afford data in the body-fixed frame of the molecule, and asymmetry in the molecular dissociation can be observed with respect to the electron direction.

Doubly excited states and their decay give rise to a multitude of narrow structures, called Fano resonances (*7*), in atomic photoionization spectra. These oscillations in the cross-section are the result of interference between two indistinguishable pathways through which the electron can be ejected. The photon can expel an electron directly, or it can promote the atom to a doubly excited state, which then decays after a delay caused by emission of one electron through autoionization. Because the final state in both of these pathways is the same, the amplitudes for each pathway must be added coherently, leading to either constructive or destructive interference, depending on the phase shift induced by the time delay. Doubly excited states have also been seen (*8*–*11*) and predicted (*12*, *13*) for molecules. However, because in molecules the excess photon energy can be distributed among internal nuclear and electron degrees of freedom, the situation is much more complex than in atoms, and a clear-cut proof of the interference effects is missing.

We clearly demonstrate such interference effects and show that they cause symmetry breaking in dissociative photoionization. A first observation of asymmetric photoelectron emission from H_2 has been reported in pioneering experiments by Lafosse *et al.* (*14*). In a different context, asymmetric electron emission has been observed in O_2 (*15*) as the result of the decay of atomic oxygen after photodissociation of the O_2 molecule. In this case, the observed asymmetry thus does not strictly arise from a molecular decay process.

We used the framework of the dipole approximation given in Dill's formula (*16*) to evaluate photoionization cross-sections that correspond to leaving the residual molecular ion in a specific electronic state α, which is differential in (i) the photoelectron energy ε, (ii) the photoelectron emission direction in the molecular frame, and (iii) the polarization direction with respect to the molecular axis. The transition matrix element involves the ground molecular state of energy W_{gv} and the final molecular state of energy $W_{\upsilon_\alpha} + \varepsilon$ representing a molecular ion in the υ_α vibronic state (either dissociative or nondissociative) and an emitted electron of energy ε. Energy conservation dictates that $W_{gv} + h\nu = W_{\upsilon_\alpha} + \varepsilon$. The two wave functions were connected by the dipole operator and were evaluated, neglecting rotational effects, in the adiabatic approximation using the theory of Sánchez and Martín (*17*). [See also equations 42 and 60 of Martín (*18*).]

Briefly, the final state comes from a close-coupling calculation incorporating contributions from the two lowest ionization thresholds of H_2 [$^2\Sigma_g^+(1s\sigma_g)$ and $^2\Sigma_u^+(2p\sigma_u)$], the six lowest

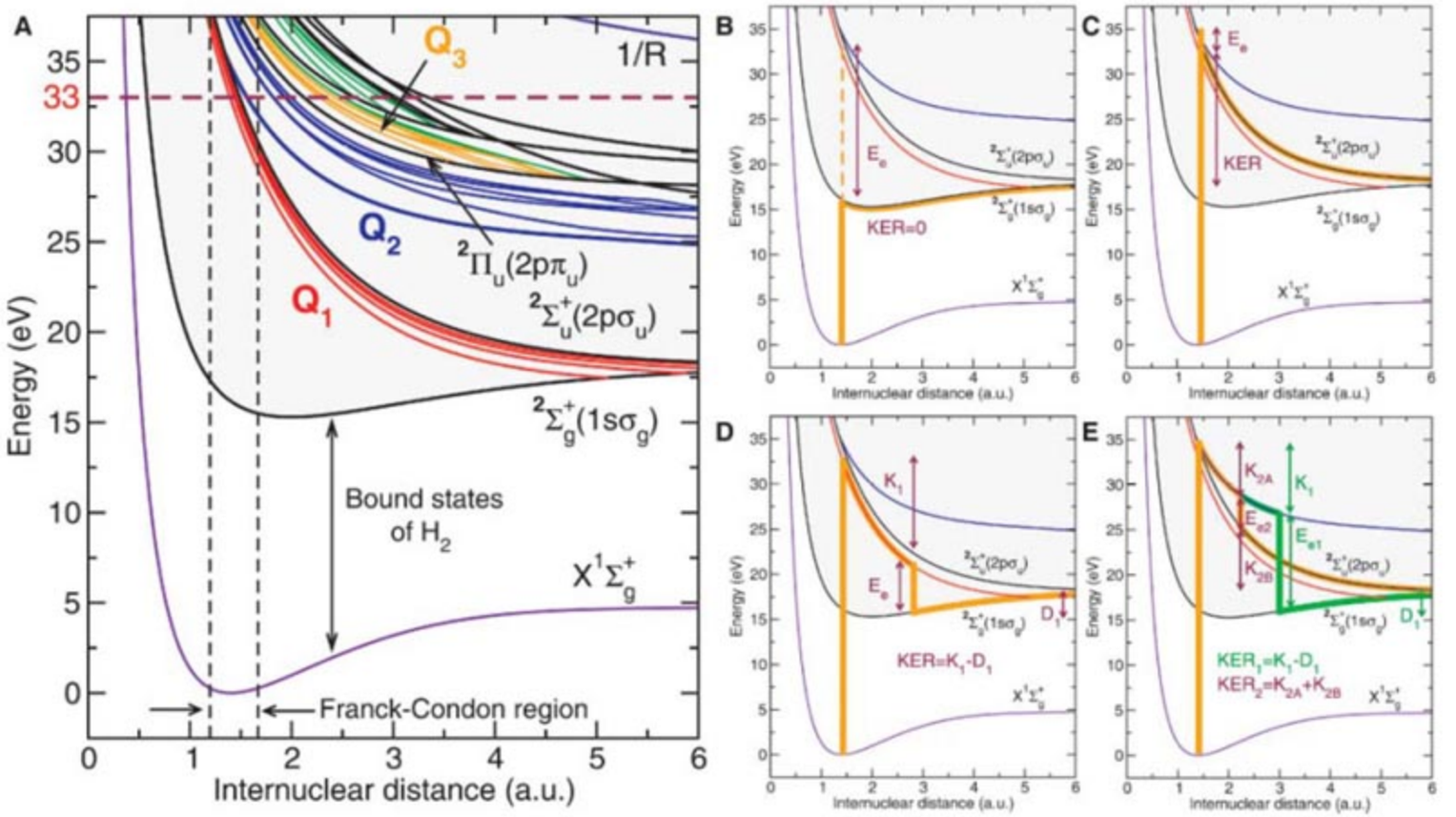

Fig. 1. Energy-level diagram and pathways to dissociative ionization. (**A**) Total energy of the H_2 and H_2^+ systems as a function of internuclear distance (a.u., atomic units). Red and blue are the lowest two series of doubly excited states of H_2 with $^1\Pi_u$ symmetry. At large internuclear distances, the Q_1 states dissociate into $H(n = 1) + H(n = 2,\ldots,\infty)$ and the Q_2 states into $H(n = 2, l = 1) + H(n = 2,\ldots,\infty)$, where n and l are, respectively, the principal and angular momentum quantum numbers of the state. (**B** to **E**) Semiclassical pathways for dissociative ionization by absorption of one 33-eV photon. (B) Direct ionization leading to $H_2^+(1s\sigma_g)$ (Eq. 2). (C) Direct ionization leading to $H_2^+(2p\sigma_u)$ (Eq. 3). (D) Resonant ionization through the lowest Q_1 doubly excited states leading to $H_2^+(1s\sigma_g)$ (Eq. 4). (E) Resonant ionization through the lowest Q_2 doubly excited states leading to $H_2^+(1s\sigma_g)$ (Eq. 5) or to $H_2^+(2p\sigma_u)$ (Eq. 6).

doubly excited states of the Q_1 and Q_2 series for both Σ_u^+ and Π_u symmetries, and the corresponding vibrational and dissociative states. At variance with dissociative states associated with bound electronic states, those associated with doubly excited states are the solutions of a complex nonlocal differential equation that includes the possibility of autoionization decay as the molecule dissociates. Therefore, the final state wave function is not given simply by the product of an electronic and a nuclear wave function but by a more complex form that accounts for interferences among the various electronic and nuclear channels. The theory is formally exact within the adiabatic and nonrotation approximations provided that all electronic and nuclear differential equations are solved exactly (*18*).

Our computational methods used B-spline functions to obtain the electronic and vibrational wave functions and are similar to methods successfully applied to a variety of other dissociation-ionization problems in H_2 (*13*, *19*, *20*). B-spline functions have also, within the fixed-nuclear approximation, led to the first numerical solution of the double photoionization of H_2 (*21*).

The experiments were performed at beamline 9.3.2 of the Advanced Light Source at Lawrence Berkeley National Laboratory. The monochromatized linearly polarized light from the synchrotron was crossed with an internally cold and localized supersonic H_2 and D_2 gas jet. The ions and electrons were directed by a combination of weak electric (20 V/cm) and parallel magnetic (10 G) fields onto two position-sensitive microchannel plate detectors with delay-line position encoding (*22*). Vector momenta were calculated from the position of impact and the times of flight of each particle. The energies of both ions and electrons were measured. Electron, ion, and neutral fragment momenta k_e, k_p^+, and k_H, respectively, are related by momentum conservation: $k_e = -(k_p^+ + k_H)$. Because of the light electron mass, the electron momentum is about 2.5% of the heavy particle momentum, leading to a nearly back-to-back fragmentation of the proton and hydrogen atom. The energy deposited by the photon ($h\nu$) in excess of the threshold for dissociative ionization (18.1 eV, Eq. 1) is partitioned among the kinetic energy release (KER) of the heavy fragments, the electron energy (E_e), and internal excitation energy (E_{exc}) of the neutral ($h\nu = KER + E_e - 18.1\ eV - E_{exc}$). As expected, the hydrogen atom is found only in the ground state ($E_{exc} = 0$) in the photon energy range that we examined. The asymptote of the $1s\sigma_g$ and $2p\sigma_u$ curve in Fig. 1 corresponds to a proton and a hydrogen atom in its ground state. Because both KER and E_e were measured for each event, energy conservation could be used to very efficiently suppress random background or proton and electron pairs from residual water molecules in the chamber. The overall energy resolution was between 100 meV and 0.5 eV, depending on the energy, and the angular resolution was about 5°. More detail on the COLTRIMS system can be found in Jahnke *et al.* (*23*).

For simplicity, we restrict our discussion to an orientation of the molecule perpendicular to the polarization axis. This orientation selects transitions from the ground state of Σ_g^+ symmetry to excited states of Π_u symmetry. Figure 2 shows the KER distribution for the reaction in Eq. 1 as a function of the photon energy. Three areas with islands can be distinguished (I, II, and III in Fig. 2B): Regions I and III can be populated by direct ionization, leaving H_2^+ in the $2p\sigma_u$ or $1s\sigma_g$ state, respectively. However, only the latter state contributes substantially, because a direct dipole transition from the H_2 ground state to the $2p\sigma_u k\pi_g$ continuum is very unlikely (*13*). [Indeed, it would be strictly forbidden in an independent electron picture, $(1s\sigma_g)^2 \rightarrow 2p\sigma_u k\pi_g$.] Thus, regions I and II cannot be reached in a single-step direct photoionization. They are the fingerprint of a delayed emission of an Auger electron from H_2 doubly excited states (either Q_1 or Q_2). These states can either dissociate as a result of the repulsive character of the corresponding potential energy curve or decay by autoionization into the $2p\sigma_u$ or $1s\sigma_g$ states when such a decay is faster than the time required for an effective dissociation.

We distinguished five different pathways, all contributing to ionization in the photon energy range of Fig. 2 and schematically shown in Fig. 1, B to E:

$$h\nu + H_2 \rightarrow H_2^+(1s\sigma_g) + e^-, \text{ direct} \quad (2)$$

$$h\nu + H_2 \rightarrow H_2^+(2p\sigma_u) + e^-, \text{ direct} \quad (3)$$

$$h\nu + H_2 \rightarrow H_2(Q_1) \rightarrow H_2^+(1s\sigma_g) + e^-, \text{ resonant} \quad (4)$$

$$h\nu + H_2 \rightarrow H_2(Q_2) \rightarrow H_2^+(1s\sigma_g) + e^-, \text{ resonant} \quad (5)$$

$$h\nu + H_2 \rightarrow H_2(Q_2) \rightarrow H_2^+(2p\sigma_u) + e^-, \text{ resonant} \quad (6)$$

Asymptotically, $H_2^+(2p\sigma_u)$ always leads to a dissociation, whereas $H_2^+(1s\sigma_g)$ can lead either to H_2^+ in a bound vibrational state or to a dissociative state. All of these pathways must be added coherently when they yield the same electron energy and hence the same KER. Their interference leads to the distinct finger-like structures in the low KER region (Fig. 2, C to F). The calculated structures (Fig. 2, C and E) are in excellent agreement with the experimental observations (Fig. 2, D and F). Our calculations show that the structure is the result of an interference between the processes in Eqs. 2 and 4, the direct and resonant pathways leading to $1s\sigma_g$

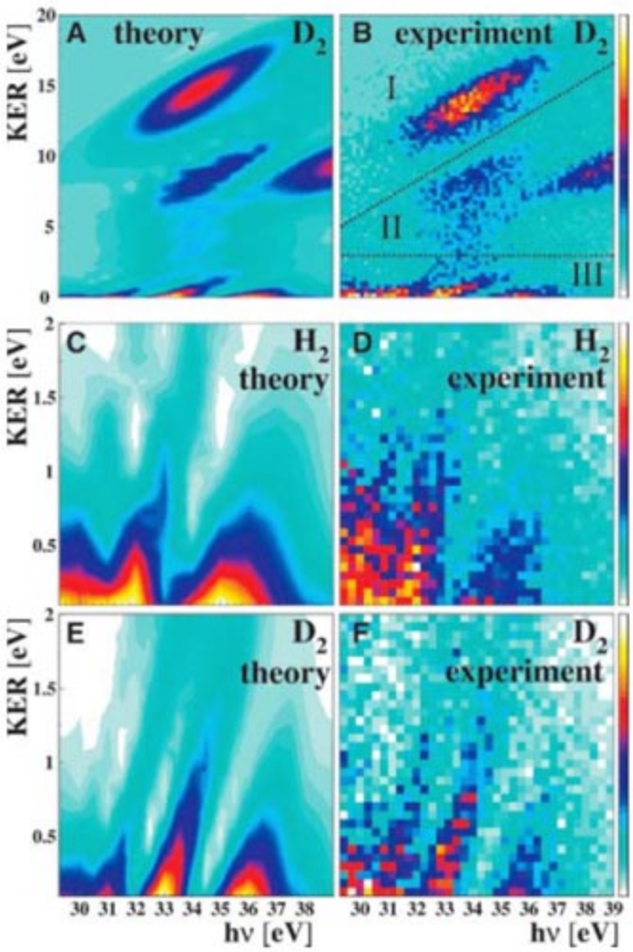

Fig. 2. Kinetic energy release as a function of photon energy for dissociative ionization of H_2 and D_2 (Eq. 1). (**A**) Theory and (**B**) experiment for D_2. Regions I, II, and III show three distinct clusters of data formed by photoionization. (**C** to **F**) Magnification of the low-KER region of panels (A) and (B) for H_2 [(C) and (D)] and D_2 [(E) and (F)]. Left, theory; right, experiment.

in the same KER region. The finger-like structures are the molecular analog of the well-known Fano interferences in the atomic case, but there are important differences entirely due to the molecular character of H_2. As the photon energy increases, the position of a particular peak shifts to higher KER, which leads to fingers with a slope approximately equal to one. The number and position of the fingers is controlled by the overlap between the dissociative states that are associated, respectively, with processes in Eqs. 2 and 4, so it is not surprising that our experimental data and calculations for H_2 and D_2 show a large isotope effect on these structures (the different masses cause distinct oscillations in the dissociative states).

We then turned to the angular distribution of the electron. We considered a photon energy of 33.25 eV and, as above, an orientation of the molecule perpendicular to the polarization axis. Figure 3 shows the key results of this work. Plotted is the angular distribution of the electron with respect to the polarization axis (horizontal). The plane of the figure is defined by the molecular axis and the polarization vector; only electrons in this plane are selected. The molecule is perpendicular to the polarization axis with the proton pointing upward. The angular distributions are found to vary strongly with the kinetic energy release. In addition to the change from a dumbbell to a butterfly shape, we found a strong asymmetry, in particular in a narrow range of $KER \cong 8$ to 10 eV, corresponding to an electron energy of $E_e \cong 5$ to 7eV. All major features predicted by our theory are confirmed by the experimental data. They are also consistent with those reported in a previous experiment (*14*) by averaging over KER intervals of 2.5 to 3 eV.

Our theoretical analysis allows us to distinguish the contributions leading to $1s\sigma_g$ (the sum of processes in Eqs. 2, 4, and 5) from those leading to $2p\sigma_u$ (the sum of processes in Eqs. 3 and 6). For a fixed photon energy of 33.25 eV, the contributions of the $1s\sigma_g$ and $2p\sigma_u$ channels overlap in the 8- to 10-eV region (Fig. 4), where the largest asymmetry is observed (Fig. 3).

How can the $1s\sigma_g$ and $2p\sigma_u$ channels interfere to produce an asymmetric angular distribution? To answer this question, we performed a model calculation in which we only included the direct ionization channels—$1s\sigma_g k\pi_u$ and $2p\sigma_u k\pi_g$—and the lowest Q_2 state of Π_u symmetry. The angular distributions found in this model calculation were very similar to those obtained from the full calculation (Fig. 3). In particular, the asymmetry was very well reproduced, showing that the Q_1 states are not responsible for its occurrence. We then excluded the two direct channels (Eqs. 2 and 3) and only considered the decay of the Q_2 state through the channels in Eqs. 5 and 6. The asymmetry remained, thus showing that the origin of the asymmetry is the interference between these two channels, i.e., between the resonant population of an ungerade and a gerade state. It is only the coherent superposition of these pathways that allows for a localization of the bound electron in the dissociating H_2^+. The transient molecule has broken symmetry and can keep a memory of the direction in which the electron departed. We also found that the fingers in Fig. 2 did not appear when the direct channel (Eq. 2) was not included in the calculation, thus confirming that their origin is the interference between resonant and nonresonant population of the $1s\sigma_g$ state. In any case, the latter interference did not lead to a noticeable asymmetry.

The results of the full quantum calculation completely differed from those of the widely used simple semiclassical model (also used in Fig. 1, B to E, for pedagogical purposes). In this simple model, the system always strictly followed the potential energy curves and only vertical transitions between them were allowed. These vertical transitions may occur as a result of photon absorption (vertical lines on the left) or autoionization decay (vertical lines on the right). In this framework, all molecules had an

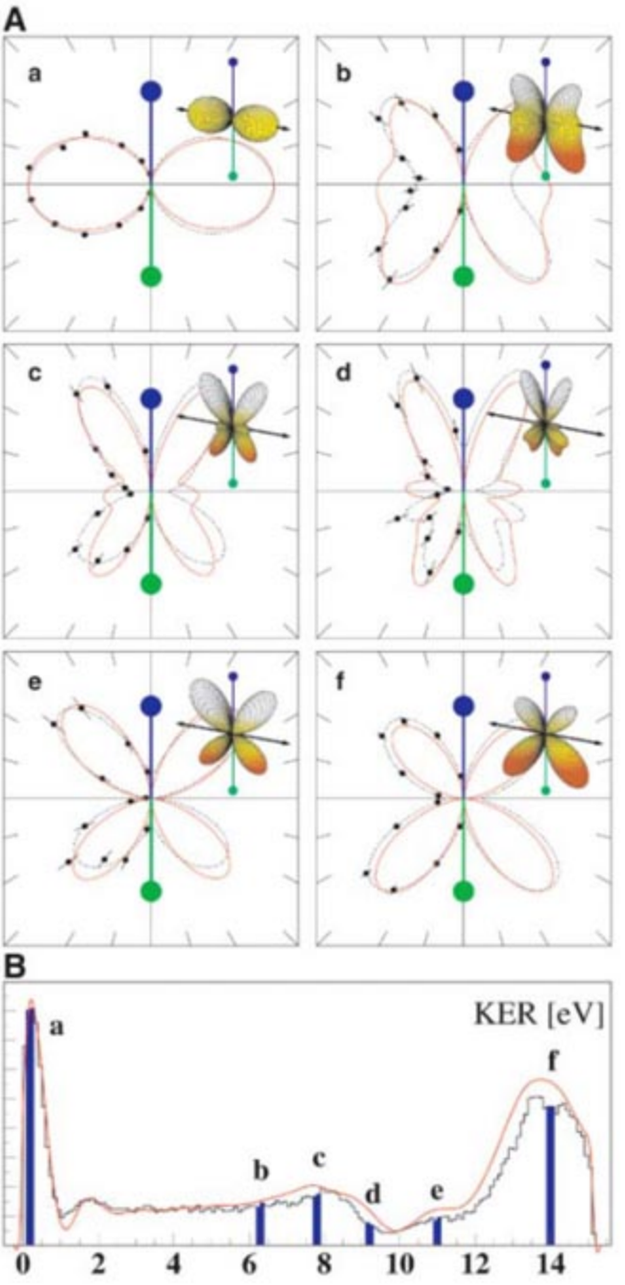

Fig. 3. (**A**) Angular distribution of the electrons as a function of KER for dissociative ionization of D_2 (Eq. 1) at a photon energy of 33.25 eV, linearly polarized light. The orientation of the molecule at 90° to the polarization (theory) and 90° ± 10° (experiment) is indicated by colored circles (blue, deuteron; green, deuterium). The (horizontal) polarization vector and the molecular axis define a common plane. The electron is restricted to this plane by ±45°. Solid red line, theory; circles with error bars (where error is SD), experiment; dotted line, fit of the experimental data with spherical harmonics. The theoretical results have been integrated over the experimental acceptance angles and KER resolution as well as electron resolution. Infinite resolution theoretical results are shown by the small three-dimensional plots in the upper right: KER = 0.2 (a), 6.3 (b), 7.8 (c), 9.2 (d), 11 (e), and 14 eV (f). Units are arbitrary units. (**B**) The angle-integrated KER spectrum. Red line, theory; black line, experiment; letters a to f correspond to a to f in (A); KER intervals are ±0.1 eV. The *x*-axis shows KER in eV. The *y*-axis shows a cross-section in arbitrary units.

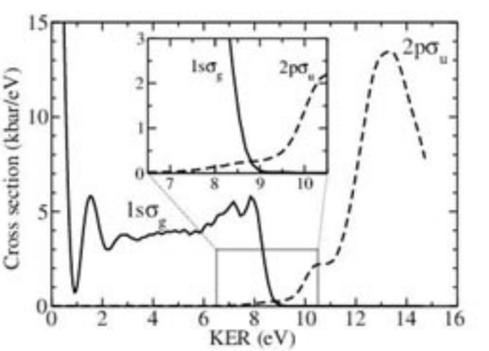

Fig. 4. Calculated D^+ kinetic energy distribution in dissociative ionization of D_2 by absorption of a 33.25-eV photon. Solid line, $1s\sigma_g$ channel; dashed line, $2p\sigma_u$ channel. The inset is a magnification of the squared region.

identically well-defined value of the internuclear distance during the transition and, consequently, any possible direct energy exchange between electronic and nuclear motions was neglected. For example, in such a model, the electron energy from the path shown by an orange line in Fig. 1E (resonant photoionization through the $2p\sigma_u$ channel) would be equal to the energy difference between the Q_2 and the $2p\sigma_u$ curve at the marked internuclear distance. Similar reasoning predicts the electron energy along the path shown by the green line (resonant photoionization through the $1s\sigma_g$ channel). Our calculations show that, in this case, although such simplified models have heuristic and pedagogical value, they lead to false conclusions. The model predicts that the maximum possible value of the KER in the $1s\sigma_g$ channel is 8.1 eV (corresponding to an autoionization decay at infinite internuclear distance), which is the minimum possible value of the KER in the $2p\sigma_u$ channel (corresponding to autoionization decay at the equilibrium internuclear distance). Therefore, no interference between g and u states can occur within this model because the electron energies and the KER regions for transitions to $1s\sigma_g$ and $2p\sigma_u$ would have no overlap, and hence the electron ejection would always be symmetric. Our fully quantum mechanical treatment showed that transitions to the $1s\sigma_g$ state can occur beyond 8.1 eV and that transitions to the $2p\sigma_u$ state are possible even at zero KER. Thus, the angular distribution can exhibit an asymmetry over the whole region of KER. Strictly speaking, a symmetric dissociation in the presence of resonances is the exception rather than the rule. It becomes quantitatively substantial in the region where both channels are comparably active, between 8 and 10 eV; however, it is also visible in regions where one of the channels dominates (Fig. 3A, b to f).

Notably, the observed asymmetry has no relation to the direction in which the charged fragment is emitted: The larger lobes are sometimes found on the ion side (Fig. 3A, c, d, and e) and sometimes on the neutral side (Fig. 3A, b and f). Both theory and experiment show that the asymmetry oscillates with the KER and that the amplitude of these oscillations is more important in the region where the $1s\sigma_g$ and $2p\sigma_u$ channels overlap. Between consecutive oscillations, there are KER values for which the distribution is practically symmetric. Thus, the asymmetry cannot be explained by a preferred attractive interaction between the proton and the escaping electron (the latter is too fast to be efficiently perturbed by the slow proton, except possibly in the region of the maximum allowed KER).

Asymmetric photoelectron angular distributions should arise in any symmetric molecule that decays through two (or more) dissociative ionization channels associated with different symmetries of the residual molecular ion. When the final electron energy is the same in both channels, the corresponding ionization pathways are indistinguishable. This equivalence leads to interferences that depend on the time delay between the two ionization processes. The time delay implies that the decay in either pathway occurs at different positions of the nuclei. This unique relationship between time delay and nuclear positions makes the problem of molecular autoionization much richer than the atomic case, and the asymmetry of the photoelectron angular distribution its most noteworthy (and so far unexpected) effect. Symmetry breaking should be considered a general molecular manifestation of autoionization when several decay channels are effectively accessible.

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Ultrafast Bond Softening in Bismuth: Mapping a Solid's Interatomic Potential with X-rays

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Intense femtosecond laser excitation can produce transient states of matter that would otherwise be inaccessible to laboratory investigation. At high excitation densities, the interatomic forces that bind solids and determine many of their properties can be substantially altered. Here, we present the detailed mapping of the carrier density–dependent interatomic potential of bismuth approaching a solid-solid phase transition. Our experiments combine stroboscopic techniques that use a high-brightness linear electron accelerator–based x-ray source with pulse-by-pulse timing reconstruction for femtosecond resolution, allowing quantitative characterization of the interatomic potential energy surface of the highly excited solid.

The availability of bright sources of ultrafast hard x-rays, such as future free-electron lasers, opens up the possibility to follow atomic motion stroboscopically with the picometer spatial and femtosecond temporal resolution required to capture the fastest atomic vibrations and the making and breaking of chemical bonds (*1*). However, the inability to precisely time the x-ray probe can lead to significant reduction in temporal resolution. Recently, the use of single-shot determination of the x-ray arrival time as a means of random sampling has been demonstrated to circumvent this problem (*2*). Using this technique, we con-

ducted femtosecond laser-pump x-ray–probe experiments that elucidate the role that carrier-induced bond-softening and anharmonicity play in the high-amplitude phonon dynamics of photoexcited bismuth.

The valence electrons and ionic cores (nucleus and core electrons) that constitute a crystalline solid, in general, can be considered as distinct components that couple through the electron-lattice interaction. In bismuth, as well as antimony and tellurium, the electron-lattice interaction is strong and the lattice configuration is sensitive to the population distribution of electrons within the conduction bands. In these materials, femtosecond photoexcitation of charge carriers drives the symmetric zone center A_{1g} coherent optical phonon mode (*3*–*5*). The vibrational excitation is generally believed to be displacive: The population redistribution of valence electrons alters the potential energy surface of the lattice and gives rise to a restoring force that drives coherent atomic motion. The dynamics of this mode are determined by the curvature and minima location of the altered potential energy surface (quasi-equilibrium coordinate). Knowledge of electronically excited energy surfaces is essential for predictive models of nonequilibrium behavior in this and a wider class of important processes in nature (from photocatalysis to nonequilibrium charge transport in nanojunctions).

Experimentally, the A_{1g} vibrational mode has been monitored indirectly by measuring time-dependent optical reflectivity (*3*, *6*–*10*) and directly by time-resolved x-ray diffraction measurements (*11*). However, with the latter technique, low x-ray flux prevented carrier-dependent studies of the interatomic potential. Recent observations in bismuth and tellurium reveal that the vibrational frequency is not constant: It red-shifts from the equilibrium value under high-intensity excitation, indicating a softened phonon mode (*7*, *9*–*12*). After the initial softening, the oscillation frequency blue-shifts back toward the equilibrium value as the oscillation amplitude and carrier density decay (*9*, *10*). The mechanism responsible for this time-dependent vibrational frequency shift, or chirp, has been controversial. Hase *et al.* concluded that the chirp was due to an amplitude-dependent frequency caused by anharmonicity of the interatomic potential (*9*). Fahy and Reis suggested an alternate explanation based on electronic softening of the potential and the subsequent dynamics of the photoexcited carriers (*13*). Optical coherent control experiments in which the phonon amplitude was varied at fixed electronic excitation demonstrated that the observed phonon frequency is dominated by electronic effects and that anharmonicity in the interatomic potential plays a negligible role, a finding that was supported by ab initio constrained density functional theory (DFT) calculations (*10*). However, because optical reflectivity does not measure atomic positions, the location of the potential energy minimum and the amplitude of the phonon-driven atomic displacement could not be determined.

We used femtosecond x-ray diffraction to elucidate the dynamics of the high-amplitude phonons by direct measurement of the atomic positions within the unit cell. The knowledge of the time evolution of the atomic positions enables the determination of the quasi-equilibrium coordinate and curvature of the interatomic potential and the comparison of these parameters to previous DFT calculations. The potential well shifts and softens with increasing carrier density, corresponding to a highly excited solid in which a substantial fraction of the total valence electrons are promoted to the conduction bands.

The room temperature structure of bismuth is rhombohedral A7 with two atoms per unit cell. This structure is a Peierls distortion of a simple cubic structure, with alternating atoms spaced nonequidistantly along the body diagonal or trigonal axis. Thus, there exists a double-well interatomic potential with normalized equilibrium coordinate at $x = 0.5 \pm \delta$ (in units of the hexagonal unit cell length, $c = 1.18$ nm). The A_{1g} mode consists of an oscillation of the two basis atoms along the trigonal direction, and thus x is also the phonon coordinate. δ is a measure of the Peierls distortion, that is, the deviation of each potential energy minimum from the symmetric $x = 0.5$ point. The quasi-equilibrium coordinate and shape of the well constraining the atoms along the trigonal direction are sensitive to excitation of carriers from the valence band to the conduction band (*10*).

A 50-nm-thick bismuth film grown by molecular beam epitaxy with a (111) surface orientation (*14*) was excited at room temperature by near-infrared pulses [(70 fs full width at half maximum (FWHM)] propagating from a Ti:sapphire laser system in a direction colinear with the x-rays. The x-ray pulses (10^6 photons at 9 keV, 0.24 mm^2 area, 100 fs duration) were generated from the Sub-Picosecond Pulse Source (SPPS) at the Stanford Linear Accelerator Center (SLAC). The (111) x-ray Bragg reflection was observed for absorbed excitation fluences between 0.3 and 3.0 mJ/cm^2 per pulse at a 10 Hz repetition rate (*15*). We note that at 1.5 mJ/cm^2, enough energy is deposited to eventually raise the temperature of the entire film to the melting point, although at least 4.1 mJ/cm^2 is required to provide the additional latent heat for thermal melting. It is in this high fluence regime that ultrafast excitation of carriers generates large-amplitude coherent phonons with a significantly lowered frequency.

During the first few picoseconds after excitation, it appears that the absorbed energy is stored almost entirely in the electronic degrees of freedom and the mechanical vibration associated with the A_{1g} mode. In this time, the volume of the unit cell remains fixed and the

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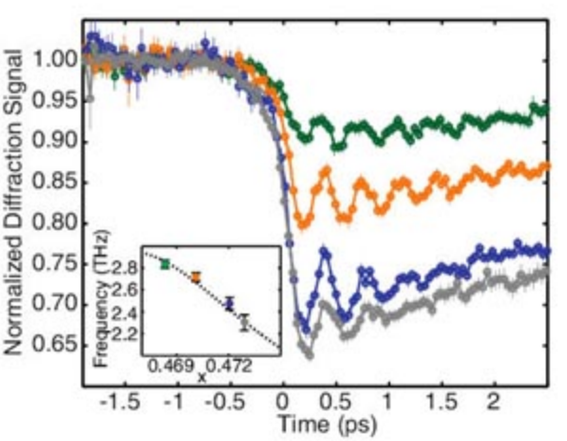

Fig. 1. Bismuth (111) x-ray diffraction efficiency as a function of time delay between the optical excitation pulse and x-ray probe for excitation fluences of 0.7 (green), 1.2 (red), 1.7 (blue), and 2.3 mJ/cm^2 (gray). The zero-delay point was set at the half maximum of the initial transient drop. The inset displays the optical phonon frequency as a function of the normalized atomic equilibrium position along the body diagonal of the unit cell x as measured by x-ray diffraction. The dotted curve represents the theoretical prediction obtained from DFT calculations of the excited-state potential-energy surface (*10*).

lattice remains at room temperature. On the time scale of ~20 picoseconds, considerable uniaxial strain is observed as a shift in the Bragg angle. Thus, the observed changes in the diffraction efficiency at these early times (Fig. 1) are due to structural changes within the unit cell of the crystal. The structure factor for the (hkl) Bragg reflection is a function of the phonon coordinate

$$F = 2f_{Bi} \cos[\pi (h + k + l) x] \quad (1)$$

where f_{Bi} is the atomic scattering factor for bismuth. In the limit of a thin film and constant temperature, the normalized diffraction signal for the (111) reflection is a direct measure of the atomic displacement along the trigonal direction

$$I(t) / I(0) = \cos^2[3\pi x(t)] / \cos^2[3\pi x(0)] \quad (2)$$

A large transient decrease in diffraction efficiency occurs upon the arrival of the excitation pulse ($t = 0$) and is followed by damped oscillations superimposed upon a recovery. In the high-symmetry, non-Peierls distorted state, $x = 0.5$ and the (111) reflection is forbidden by symmetry. Thus, the transient decrease is attributed to a sudden shift in the minima location of the potential energy surface (toward $x = 0.5$) in the excited electronic state, leading to atomic oscillations about the shifted equilibrium. Measurements of the (222) reflection, which increases in intensity for the higher-symmetry arrangement, confirm this attribution. A similar behavior was observed by Sokolowski-Titen *et al.* (*11*). The quasi-equilibrium coordinate is then measured directly from the magnitude of the transient decrease of the relative diffraction efficiency seen in the (111) data (i.e., from the value about which the oscillations occur). The subsequent increase is ascribed to carrier relaxation through diffusion and recombination, which eventually restores the potential energy surface to its equilibrium shape at excitation levels below the damage threshold.

The oscillatory part of the diffraction signal, corresponding to the coherent optical phonon mode, was fit to a decaying sinusoid with fixed frequency and varying initial phase. Because the phonon frequency is chirped, the frequency obtained from the fit represents the average phonon frequency over the fitting interval (~0.5 to 1.5 ps). The measured value, ranging from 2.84 to 2.31 THz, is red-shifted relative to that observed in continuous wave Raman scattering experiments (2.93 THz) (*8*). Similar softening has been measured in optical experiments (*7*, *9*, *10*).

The inset of Fig. 1 displays the dependence of phonon frequency on the quasi-equilibrium coordinate (measured over the same time interval as the phonon frequency). Our results also represent average values over the sample depth for both frequency and quasi-equilibrium coordinate, because the x-ray penetration depth is much larger than the film thickness. In the absence of photoexcitation, the accepted values of the frequency and equilibrium location at room temperature are 2.93 THz and $x = 0.46719$ (*10*, *16*–*18*). At a measured quasi-equilibrium coordinate of $x = 0.4729 \pm 0.0001$, the well is shifted by 6.7 picometers and the interatomic forces are softened by 35% (~20% decrease in the phonon frequency). The results are compared with the constrained DFT calculation of Murray *et al.* (*10*) (dotted line). These first-principles calculations assumed production of a single electron-hole pair per absorbed photon and rapid thermalization of the electrons and holes by intraband scattering, followed by electron-hole recombination on a longer time scale. Therefore, the electron and hole distributions are approximated as independent Fermi-Dirac distributions with separate chemical potentials such that the average energy of each pair is equal to the photon energy. Despite these approximations, the excellent agreement with experimental results here demonstrates the ability of DFT to quantitatively predict the essential excited-state features (quasi-equilibrium coordinate and frequency) of this system.

Under the same assumption of a single electron-hole pair produced per absorbed photon, we separately compare the measured quasi-equilibrium coordinate as a function of carrier density to the DFT predictions (Fig. 2). The calculated double-well potential with the quasi-equilibrium coordinate is indicated by the dotted line (for illustrative purposes we arbitrarily chose the $x < 0.5$ well). The curving of the dotted line toward $x = 0.5$ shows that increasing carrier density reduces the Peierls distortion. The shift in equilibrium coordinate was measured for carrier densities spanning 0.18% to 1.8% of the total valence electrons, averaged over the 50-nm film. A transient displacement of 11 picometers was observed for the highest carrier density and corresponds to 2.0% of the equilibrium interatomic separation along the trigonal axis. This value is not the same as the change in nearest-neighbor distance, which is smaller by a factor of about two. Higher excitation levels led to irreversible damage to the material, which was evident as an overall decrease in the diffraction efficiency for the unexcited crystal.

The calculations suggest that upon excitation of ~2.5% of the valence electrons, bismuth undergoes a structural phase transition to a higher symmetry state, whereas at approximately 2% excitation the barrier between the wells is lowered sufficiently for the atoms to move in both wells (*19*). It is unclear, for an initial room temperature lattice, whether this level of excitation density can be achieved without subsequent thermal melting of the material (or what role formation of domains plays in the melting transition). At these excitation levels there is no

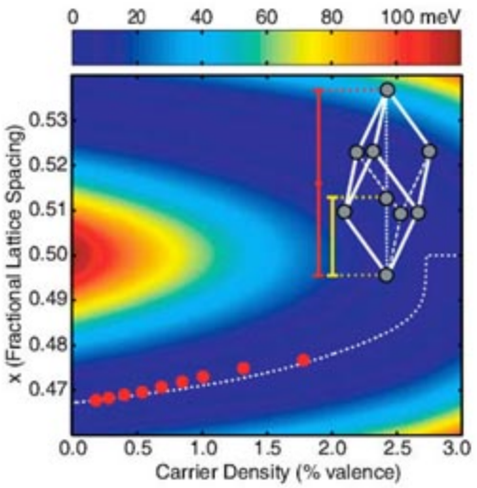

Fig. 2. Interatomic quasi-equilibrium position as a function of the percentage of valence electrons promoted into the conduction band. The red circles represent experimental results; the dotted line depicts the potential minimum obtained from the DFT potential landscape. The adjusted potential energy surface obtained from DFT is overlayed in false color representation (*10*). The bismuth unit cell is displayed in the upper right quadrant. The red bar represents the body diagonal length *c*, and the yellow bar represents the basis atom coordinate *xc*.

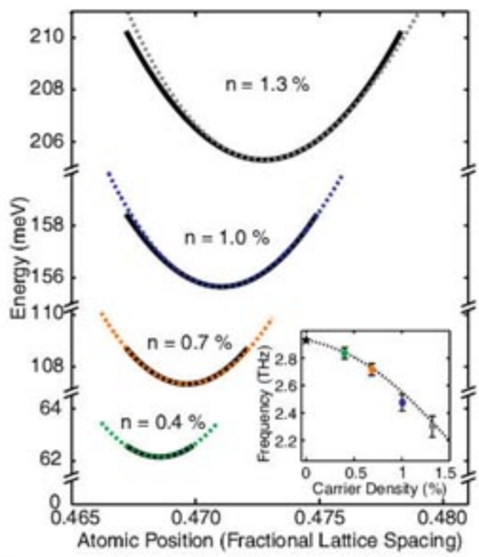

Fig. 3. Interatomic potential curvature as a function of carrier density *n*. Solid lines represent the region of the interatomic potential sampled by the atoms under complete displacive excitation. The curvature was derived from the measured phonon frequency, assuming pure harmonic motion. Dotted lines are cross sections of the DFT interatomic potential surface displayed in Fig. 2 for fixed carrier densities. The vertical scale is adjusted for clarity, and the potential energy is displayed relative to the minimum of the unexcited structure. The inset displays the phonon frequency as a function of carrier density. The dotted line shows *A1g* frequencies from DFT frozen phonon calculations. The starred point is the equilibrium Raman value of the A1g frequency.

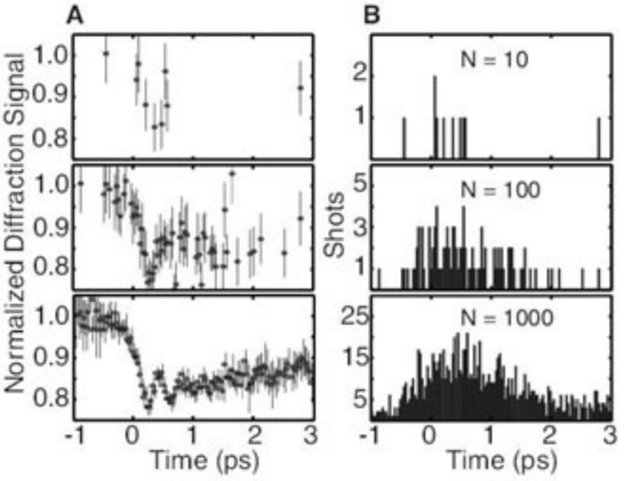

Fig. 4. (**A**) X-ray data arranged sequentially by the arrival time determined by electro-optic sampling for N = 10, 100, and 1000 shots. (**B**) Corresponding histograms of the measured electron bunch arrival times. A movie of the data acquisition is included as supporting online material.

evidence, either experimentally or in the DFT results, of a nonthermal melting transition such as that found in tetrahedrally bonded semiconductors (*20*–*24*).

In addition to the quasi-equilibrium coordinate, we extract the carrier density–dependent curvature of the potential well from the measured frequency of the $A1g$ mode, assuming a harmonic potential (solid black curves in Fig. 3). The extent of the curves represents the maximum range of motion of the ions that occurs in the limit of a purely displacive excitation. A comparison of these results with the potential calculated by DFT (dotted lines, corresponding to fixed-density cross sections of the surface shown in Fig. 2) shows that for carrier densities as high as 1%, the atoms are well described as moving in a purely harmonic potential. At the highest carrier density in which we could extract a phonon frequency from the data, the calculations predict only a slight deviation from a harmonic potential. This result is reinforced by the excellent agreement between the measured and calculated frequency (which includes the anharmonic terms) as a function of carrier density (Fig. 3, inset). Thus, although anharmonicity must be present at some level, electronic softening by far dominates the determination of the phonon frequency at the high excitation densities in this and former experiments.

Two important technical advances enabled these experiments: the generation of high x-ray photon flux in a temporally short pulse from a linear accelerator source and the ability to measure the relative x-ray and laser pulse arrival times. Standard stroboscopic measurements in the subpicosecond time regime derive the excitation pulse and probe pulse from the same ultrafast source with the pump-probe relative delay determined by the optical path length difference. This setup ensures synchronization between pump and probe and realizes the temporal limit set by the probe pulse duration. In experiments in which the pump and probe are derived from separate sources, such as the study reported here, synchronization is not inherent and must be actively attained. To achieve temporal resolution of the order of x-ray pulse duration, it is necessary to either synchronize the two sources to a fraction of the probe pulse duration or to measure the relative arrival time on a shot-by-shot basis. As a result of sources of jitter in the linear electron accelerator that cannot be mitigated, particularly electron bunch energy fluctuations, synchronization to the level of the x-ray pulse duration is not achievable and a relative time-of-arrival measurement is essential for experiments that require multishot data acquisition.

Temporal resolution of ~100 fs, required to observe coherent phonon motion in bismuth, was achieved by measuring the relative arrival time of the electron bunches using electro-optic sampling (EOS) (*2*). Laser pulses, split from the same source used to photoexcite the bismuth film, were transported by optical fiber to the electron beam (*25*). The measured electro-optic signal from the electron bunch was as short as 170 fs FWHM, and the centroid of this feature was determined to sub-20 fs precision and used as a time stamp for the relative time of arrival. The temporal jitter between the pump and the probe provided random sampling of time points. X-ray data obtained from diffraction measurements were sorted into 40-fs time bins according to the time of arrival measured through EOS (Fig. 4). Data within a time bin were averaged together to increase the signal-to-noise ratio. The results of these experiments demonstrate the type of data collection techniques and timing diagnostic that will be instrumental to maximize the scientific capabilities of the next generation of x-ray light sources.

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Supporting Online Material

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Movie S1

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Rapid 20th-Century Increase in Coastal Upwelling off Northwest Africa

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Near-shore waters along the northwest African margin are characterized by coastal upwelling and represent one of the world's major upwelling regions. Sea surface temperature (SST) records from Moroccan sediment cores, extending back 2500 years, reveal anomalous and unprecedented cooling during the 20th century, which is consistent with increased upwelling. Upwelling-driven SSTs also vary out of phase with millennial-scale changes in Northern Hemisphere temperature anomalies (NHTAs) and show relatively warm conditions during the Little Ice Age and relatively cool conditions during the Medieval Warm Period. Together, these results suggest that coastal upwelling varies with NHTAs and that upwelling off northwest Africa may continue to intensify as global warming and atmospheric CO_2 levels increase.

Coastal upwelling occurs along the eastern margins of major ocean basins and develops when predominantly alongshore winds force offshore Ekman transport of surface waters, which leads to the ascending (or upwelling) of cooler, nutrient-rich water (*1*). Coastal upwelling is of large economic importance and accounts for ~20% of the global fish catch, yet constitutes <1% of the world's oceans by area (*2*). Coastal upwelling is also of major importance to primary and secondary productivity and strongly influences atmosphere-ocean CO_2 exchange, as well as carbon recycling and export to the open ocean. The understanding of potential global warming–related changes in the intensity of coastal upwelling has become increasingly important because of the likelihood of dramatic ecosystem and socioeconomic impacts (*3*–*6*). Although there is some evidence that the vigor of coastal upwelling, at least at the decadal scale, has progressively increased as a result of anthropogenic greenhouse gas emissions (*3*, *5*, *7*), most evidence is based only on short instrumental records. Longer temporal records are needed to assess whether upwelling truly has intensified.

We investigated long-term changes in coastal upwelling intensity along the northwest (NW) African margin using two sediment cores that not only have decadal-or-better resolution but also extend from the late Holocene to the end of the 20th century and overlap temporally with instrumental data sets. The two cores (gravity core GeoB6008-1 and multi-core GeoB6008-2) were recovered from the heart of the Cape Ghir upwelling system off the coast of Morocco (30°50.7′N, 10°05.9′W; 355-m water depth) (Fig. 1). The region off Cape Ghir is particularly well suited for the study of upwelling because it constitutes one of the most persistent upwelling cells along the NW African coast, with upwelling occurring year-round (*8*–*10*). Sea surface temperatures (SSTs) in upwelling zones are sensitive indicators of changes in upwelling intensity and prevailing winds (*8*, *11*), and, in the Cape Ghir area, cooler SSTs result directly from increased upwelling intensity (*8*, *10*) (Fig. 1). Thus, using the well-established alkenone unsaturation index ($U^{K'}_{37}$) as a SST proxy, we reconstructed SST and upwelling at Cape Ghir (*12*). We have confidence in the use of alkenone $U^{K'}_{37}$ as an SST proxy at Cape Ghir because several factors that could have a potentially detrimental influence on the $U^{K'}_{37}$-SST relationship are minimized at this site [see supporting online material (SOM) text]. We also measured the carbon isotope ratio ($\delta^{13}C$) of the benthic foraminifera *Uvigerina mediterranea* in both cores (*12*) to obtain a record of anthropogenic carbon input into the ocean as recorded at site GeoB6008.

When taken together, dating of the sediment cores shows that they extend from 520 B.C. to 1998 A.D. (*12*). ^{210}Pb dating on the 33-cm-long multi-core and the upper 17 cm of the gravity core (Fig. 2 and fig. S1), in addition to eight calibrated accelerator mass spectrometer (AMS) radiocarbon analyses on the rest of the gravity core (Fig. 3A and table S1), reveals an extremely high sedimentation rate of ~210 cm per thousand years (*12*). This finding, along with a sampling resolution of between 2 and 25 years, allows an unprecedented view of 20th-century and late-Holocene upwelling history.

For most of the 20th century, the two alkenone SST reconstructions show a steady cooling trend of ~1.2°C, which indicates an increase in upwelling intensity (Fig. 2). In addition, the patterns of variability during the ~60-year period where the two cores overlap (1912 to 1971 A.D.) are notably similar, which attests to the consistency of the age model in this part of the core and of the SST signal in each record. The trend to cooler SSTs and increased upwelling through the 20th century is consistent with pronounced upwelling intensification for the latter part of the 20th century inferred from two calculated upwelling indices for the Canary Current region (*3*, *13*). Our SST changes are also consistent with increased, upwelling-favorable meridional wind speed observations for Cape Ghir (Fig. 2) and for the grid squares to the immediate north and south of the cape along the Moroccan coast (not shown) (*14*). Direct comparison of the alkenone SSTs with instrumental SST records is difficult because ships of opportunity (i.e.,

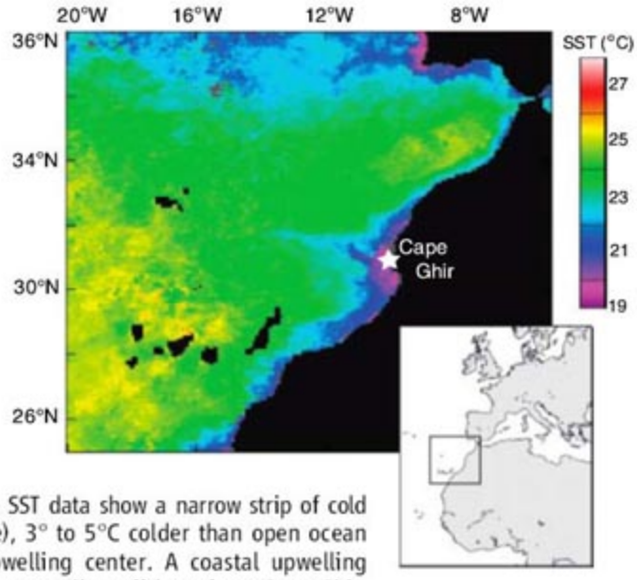

Fig. 1. Advanced very-high-resolution radiometer (AVHRR) Oceans Pathfinder 5 SST image of NW Africa (September 2004), marked with the location of sediment cores GeoB6008-1 and GeoB6008-2 (star symbol). Inset map shows the area covered by the SST image (black box). The SST image was obtained through the online POET tool [Physical Oceanography Distributed Active Archive Center (PO.DAAC) Ocean Earth Science Information Partner] at PO.DAAC, National Aeronautics and Space Administration, Jet Propulsion Laboratory, Pasadena, CA (http://podaac.jpl.nasa.gov/poet). The SST data show a narrow strip of cold coastal waters (purple and dark blue), 3° to 5°C colder than open ocean SSTs, indicating the Cape Ghir upwelling center. A coastal upwelling filament (light blue) is also present, extending offshore from Cape Ghir.

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commercial vessels that have agreed to collect oceanographic data en route to their destination) in this region pass too far from the coast to detect the upwelling (*8*, *11*), and gridded data sets smooth out the cooler upwelled-water SST signal. The absolute alkenone SST values are, however, within the range of SSTs reported by research cruises in the Cape Ghir region (SOM text). In addition, the trend to cooler SSTs at Cape Ghir is consistent with a trend to cooler SSTs for 1982 to 2001 A.D. based on satellite-derived observations for coastal upwelling along the Iberian margin (37° to 42°N) and the NW African margin (22° to 30°N and 12° to 20°N) (*15*).

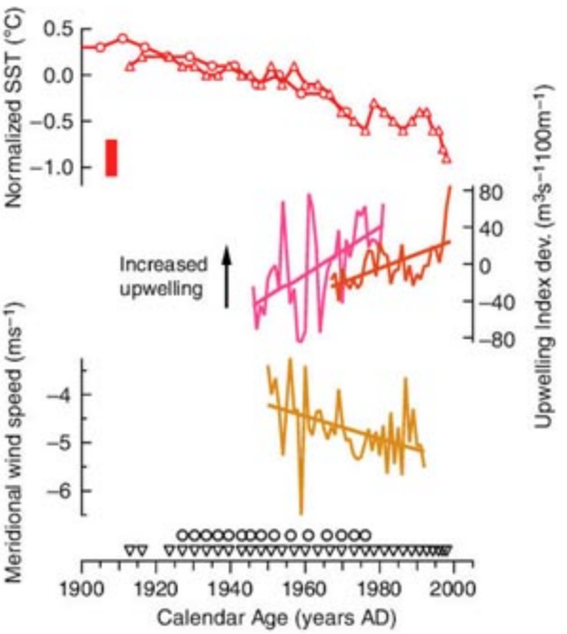

Fig. 2. Normalized alkenone SST records from cores GeoB6008-1 (red circles) and GeoB6008-2 (red triangles) for the 20th century as compared with the Bakun upwelling index for NW Africa (pink trace) (*3*), an upwelling index calculated for Cape Ghir (brown trace), and meridional wind speed data (orange trace) (*14*). Alkenone SST records are normalized to the mean for the overlapping period between them (1912 to 1971 A.D.) to allow for a ~0.5°C offset (*12*). The vertical red bar indicates the error on alkenone SST estimates (*12*). ^{210}Pb dates for GeoB6008-1 (black circles) and GeoB6008-2 (black triangles) are shown at the base of the graph. The Cape Ghir upwelling index was calculated for 31°N, 10.5°W, with a coastal angle of 182°, and was obtained from the Environmental Research Division of the National Oceanic and Atmospheric Administration, National Marine Fisheries Service, Southwest Fisheries Science Center (www.pfel.noaa.gov/) (*13*). Both upwelling indices are presented at annual resolution and as the deviation from the mean of each record. Meridional wind speed data are from Comprehensive Ocean-Atmosphere Data Set Release 1 data (*14*) for 31°N, 11°W. Calculations were restricted to the 1950–1992 A.D. period, because during this time interval no more than two values per year were missing. Annual means were then calculated based on the monthly values. More negative values indicate more southerly (equatorward), upwelling-favorable winds.

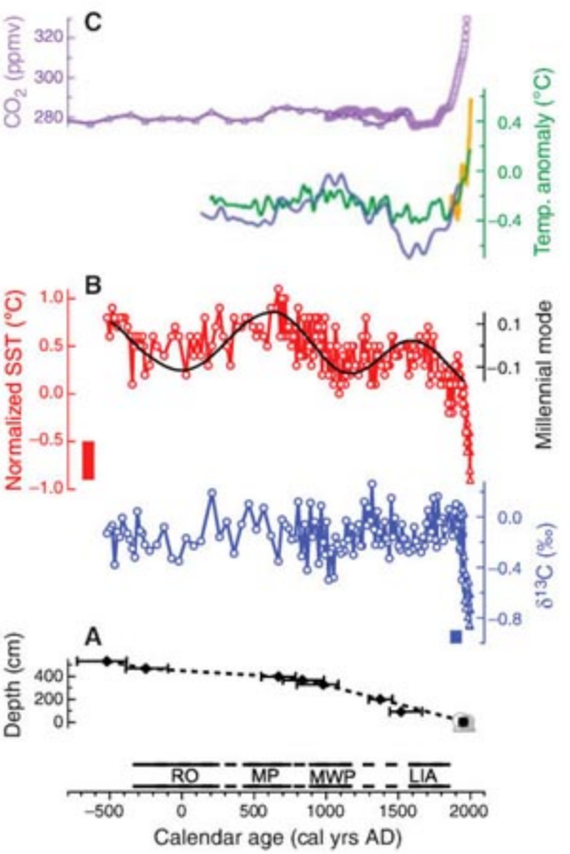

Fig. 3. Age/depth relationship, normalized alkenone SST, and δ^{13}C records for the full length of cores GeoB6008-1 and GeoB6008-2, compared with NHTA reconstructions and ice-core CO_2 records. (**A**) Age model for GeoB6008-1 based on the calibrated AMS ^{14}C ages [diamonds; ages are reported as calibrated radiocarbon years A.D. (cal yrs AD), and error bars represent the 2σ-calibrated age range (*12*)] and, at the top of the core, ^{210}Pb dates (gray circles, shown in more detail in Fig. 2), and the age model for GeoB6008-2 based on ^{210}Pb dates only (gray triangles, shown in more detail in Fig. 2). Periods highlighted at the base of the figure represent the LIA, MWP, Migration Pessimism (MP), and the Roman Optimum (RO). (**B**) Normalized alkenone SST from GeoB6008-1 (red circles) and GeoB6008-2 (red triangles), the reconstructed millennial mode from the GeoB6008-1 alkenone SST record (solid black line), and δ^{13}C measured on *U. mediterranea* from GeoB6008-1 (blue circles) and GeoB6008-2 (blue triangles). Vertical red and blue bars indicate the error on alkenone SST estimates and δ^{13}C analyses, respectively (*12*). (**C**) Law Dome (purple squares) (*28*) and Taylor Dome (purple triangles) (*29*) atmospheric CO_2 records, as well as three NHTA reconstructions: the instrumental record (10-point smoothing; orange line) (*26*), a ~2000-year reconstruction based predominantly on terrestrial proxies (green line) (*24*), and a ~2000-year reconstruction with the use of high- and low-resolution proxy data (blue line) (*25*). ppmv, parts per million by volume.

When viewed in the context of the SST anomaly reconstruction from the entire gravity core for the past 2500 years (Fig. 3B), the final 100 years of the record clearly show the strongest decrease in SST (corresponding to an increase in upwelling), which is larger and more rapid than any other change in the record. The period from 1965 to 1998 A.D. is particularly cold and is ~0.5°C colder than the next coolest 35-year period (1845 to 1880 A.D.) [mean SST anomaly from 1965 to 1998 A.D. = –0.52° ± 0.05°C (SEM), n = 15, where n is the number of alkenone SST anomaly values for the given period; mean SST anomaly from 1845 to 1880 C.E. = –0.06° ± 0.05°C (SEM), n = 7].

The GeoB6008-1 alkenone SST record also shows pronounced millennial-scale variability during the past 2500 years (Fig. 3B). This variability is highlighted through reconstruction of the long-term mode, based on the 2nd and 3rd quasi-periodic components identified through singular spectrum analysis of the GeoB6008-1 SST record (*12*) (table S2). The reconstructed millennial mode for GeoB6008-1 shows local SST maxima at ~600 and 1600 A.D. and SST minima at ~0 B.C./A.D. and 1150 A.D. (Fig. 3B). All of these extremes correspond to inferred periods of warming and cooling in the Northern Hemisphere, the most recent of which being the Medieval Warm Period (MWP) and Little Ice Age (LIA) (*16*) (Fig. 3B).

The δ^{13}C record of the benthic foraminifer *U. mediterranea* (Fig. 3B) supports the age model of our core and also suggests the presence of anthropogenic CO_2 for the most recent part of the record (SOM text). Carbon isotope values substantially decrease with respect to the past 2500 years at the beginning of the 20th century. This decrease reflects the so-called "oceanic Suess effect": the oceanic uptake of isotopically light CO_2 released by the burning of fossil fuels (*17*) (Fig. 3C). Recent estimates of the magnitude of the oceanic Suess effect are between 0.7 and 0.9 per mil (‰) up to the early 1990s, for both tropical Atlantic and Arctic Ocean surface waters (*18*, *19*). This range is consistent with the observed 20th-century decrease of ~0.8‰ in the carbon isotopic composition of *U. mediterranea*. The presence of an anthropogenic signal in the δ^{13}C record confirms that the upper part of the cores spans the 20th century, as suggested by the ^{210}Pb-dating results. Furthermore, the strong covariance between δ^{13}C and alkenone

SST records for the 20th century suggests an influence of global warming on the temperature evolution and upwelling intensity at site GeoB6008.

The rapid 20th-century cooling at Cape Ghir also coincides with the rise in atmospheric CO_2 (Fig. 3C) and likely reflects the influence of CO_2 on the land-sea thermal contrast in NW Africa and, in turn, on the alongshore winds driving the upwelling. According to the mechanism proposed by Bakun (*3*), increased atmospheric CO_2 concentration could lead to warmer surface air temperatures (SATs) over land relative to those over the ocean, particularly at nighttime when radiative cooling is suppressed by the blocking of outgoing longwave radiation by CO_2. The increased SAT deepens the thermal low-pressure cell over land while a higher-pressure center develops over the slower-warming ocean waters. The winds blow clockwise around the high and anticlockwise around the continental low. The coast represents the boundary separating the two centers. Therefore, along the coast, the wind is oriented alongshore and southward (equatorward), which thus drives the upwelling and negative SST anomalies.

The proposed mechanism is feasible to explain the increase in upwelling off Cape Ghir. At seasonal-to-interannual time scales, the pressure gradient between the coastal Atlantic and NW African continental interior was found to correlate with cooler NW African coastal SSTs and increased upwelling (*9*). At decadal time scales, analysis of global mean SAT records from 1950 to 1993 A.D. shows an increase in minimum air temperatures and a decrease in the diurnal temperature range over northern Africa (*20*), which would facilitate an increase in the land-sea pressure gradient. In addition, during the late 20th century, warmer SATs over the Saharan landmass and Eurasian continent were found to correlate with lower mean sea-level pressure over the Saharan landmass (the Sahara Low) (*21*). The Sahara Low is expected to further deepen with increased CO_2 (*21*). Deepening of the Sahara Low could enhance the land-sea pressure difference, leading to further intensification of upwelling.

Site GeoB6008 could also be influenced by the Arctic Oscillation/North Atlantic Oscillation (AO/NAO) (*22*) through its impact on the Azores High. However, the strong trend to cooler Cape Ghir SSTs and the overall weak-to-nonexistent trend in the AO/NAO for much of the 20th century (*23*) would suggest that the AO/NAO is not the dominant factor that influences the upwelling.

The normalized Cape Ghir SST anomaly record, which includes the rapid temperature changes of the past century and the millennial-scale variability, covaries with Northern Hemisphere temperature anomaly (NHTA) reconstructions (*24*–*26*), though with the opposite sign, showing a reverse "hockey stick" pattern (Fig. 3, B and C, and table S2). For example, from 1450 to 1850 A.D. (i.e., the extent of the LIA), relative warmth is observed in the GeoB6008 SST record when compared with relative cooling in the NHTA records. The antiphased behavior is an unexpected result, given the large regional variability captured from different locations by the proxy records used in the NHTA reconstructions as compared to the variability of alkenone SST record, which is a point-recorded time series. The link, however, between NHTA reconstructions and upwelling could come through the land-sea thermal contrast proposed above. The millennial-scale, hemispheric temperature variations could manifest as a greater change in land SAT as compared to SATs over the ocean, which may affect land-sea pressure gradients, alongshore winds, and therefore upwelling.

Upwelling processes, in general, may be sensitive to increased levels of CO_2. Our results of intensified 20th-century upwelling off the NW African coast also indicate a sensitivity of upwelling to SAT. Other recent findings show increased 20th-century Arabian Sea upwelling, which is attributed to global warming–related heating of the Eurasian landmass (*5*, *7*). There is also evidence for increased upwelling along the Iberian margin (*3*, *15*) and parts of the California Current and Peru-Chile Current systems (*3*, *27*) as a result of higher CO_2 levels (*3*). Given the apparent overall sensitivity of upwelling during the 20th century to increases in CO_2 and our paleo-results of a distinct upwelling response to hemispheric-scale warming and cooling, these results strongly imply that upwelling may continue to intensify with future increased levels of atmospheric CO_2 and global warming.

Upwelling regions, including Cape Ghir, show extremely high levels of biological activity, yet the ecosystem response to upwelling in these regions is dependant on a complex balance of temperature, ocean chemistry, ocean circulation, and fishing pressure (*6*). Given the importance of these marine ecosystems, our dependence on these highly valuable fisheries, and the potential role of upwelling in the drawdown of atmospheric CO_2, further understanding of climate feedbacks in upwelling regions and the ecological and socioeconomic repercussions is an imperative.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/637/DC1
Materials and Methods
SOM Text
Fig. S1
Tables S1 and S2
References

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Species Interactions Reverse Grassland Responses to Changing Climate

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Predictions of ecological response to climate change are based largely on direct climatic effects on species. We show that, in a California grassland, species interactions strongly influence responses to changing climate, overturning direct climatic effects within 5 years. We manipulated the seasonality and intensity of rainfall over large, replicate plots in accordance with projections of leading climate models and examined responses across several trophic levels. Changes in seasonal water availability had pronounced effects on individual species, but as precipitation regimes were sustained across years, feedbacks and species interactions overrode autecological responses to water and reversed community trajectories. Conditions that sharply increased production and diversity through 2 years caused simplification of the food web and deep reductions in consumer abundance after 5 years. Changes in these natural grassland communities suggest a prominent role for species interactions in ecosystem response to climate change.

Impacts of recent climate change on plants and animals are already evident, as geographic distributions shift poleward (*1*, *2*) and toward higher elevations (*3*, *4*), phenological events advance in time (*5*–*7*), and some species disappear altogether (*8*). With further climate change still expected, prediction of future impacts has become critical to conservation planning and management. To forecast ecological change under continued climate warming, however, we need a better understanding of the relative importance of direct responses by individual species to climate versus responses mediated by changing interactions with resources, competitors, pathogens, or consumers (*9*–*14*). We imposed projected future precipitation regimes over grassland in northern California to evaluate the importance to ecosystem response of direct effects on grassland species versus indirect effects arising from species interactions.

Much of the California coastal region experiences a Mediterranean climate, characterized by wet winters and long summer droughts. Ecological responses to climate change in regions with Mediterranean climate regimes may be strongly driven by the redistribution of water in time and space (*15*). Changes in seasonal water availability that affect plant phenology, for example, could lead to temporal mismatch between resource availability and consumer demand (*16*), which can have important effects on resource flow and ecosystem function (*17*). General circulation models developed at the Hadley Centre for Climate Prediction and Research (HadCM2) and the Canadian Centre for Climate Modeling and Analysis (CCM1) (*18*) predict substantial increases in precipitation over most of California but differ in the projected seasonality of these increases. The Hadley model calls for all additional rain to fall during the current winter rainy season, whereas the Canadian model projects increased rainfall extending into the current summer drought. The discrepancy between the two scenarios may be critical to the fate of grassland ecosystems in California, where summer drought severely constrains plant growth and the timing of rainfall is more important to annual production and species composition than the amount (*19*–*22*).

In 2001, we began a large-scale rainfall manipulation in a northern California grassland to examine the consequences of these two projected regimes for production and diversity of grassland plants and invertebrates. In a grassland at the Angelo Coast Range Reserve in Mendocino County, California (39° 44′ 17.7″ N, 123° 37′ 48.4″ W), 18 circular 70-m^2 plots were subjected to one of three watering treatments: a winter addition of water (January through March), a spring addition of water (April through June), and an unmanipulated ambient control (Fig. 1). Each watered plot received about 44 cm of supplementary water over ambient rainfall per year, roughly a 20% increase over mean annual precipitation but within natural variability in both amount and timing at the study site (fig. S1). We

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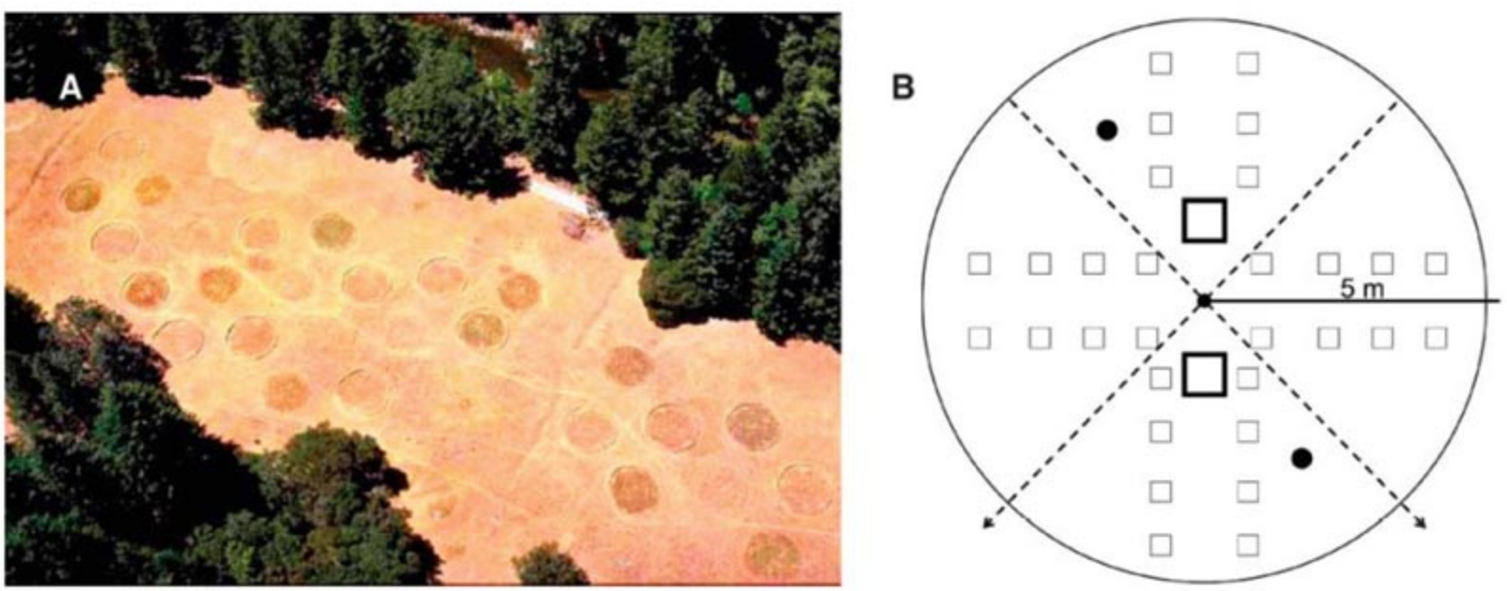

Fig. 1. (**A**) Bird's-eye view of experimental communities in July 2002. A nearby road is visible as a gray strip, top right. Research described here is from 18 open-grassland plots (18 additional plots were used in separate research). (**B**) Schematic representation of an experimental plot, shown as partitioned for measurement of plant biomass (30 900-cm^2 subplots, small squares), plant species richness (two 2500-cm^2 subplots, large squares), foliar and flying invertebrates (two perpendicular sweep-net transects, dashed arrows), and ground-dwelling invertebrates (two pitfall traps, circles) (not to scale). Detailed methods are available online (*23*).

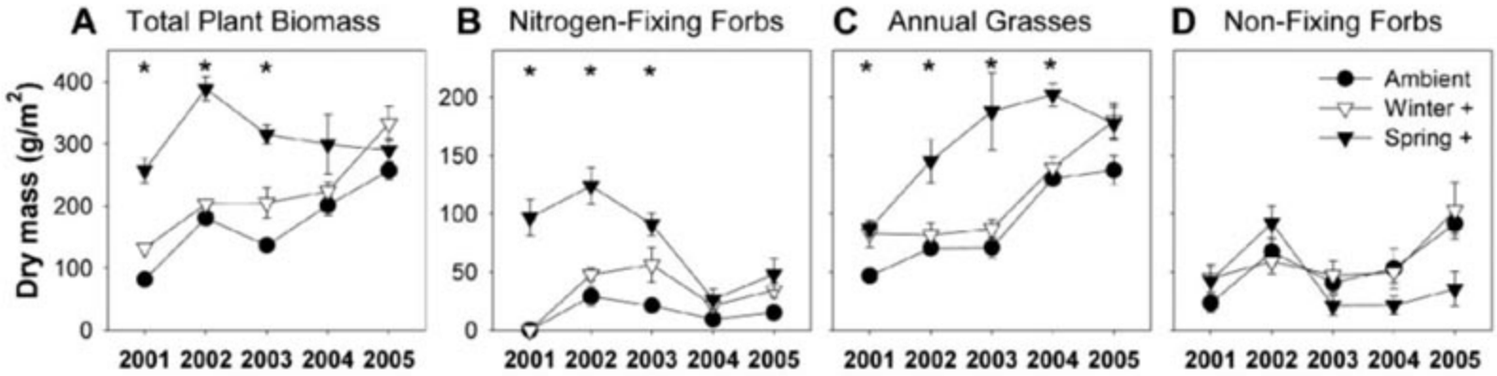

Fig. 2. Watering treatment effects on (**A**) total plant biomass and (**B** to **D**) biomass of individual plant groups (note difference in scales). Data represent treatment means ± 1 SE. An asterisk denotes a statistically significant treatment difference after Bonferroni correction for multiple comparisons. See table S1 for factor significance.

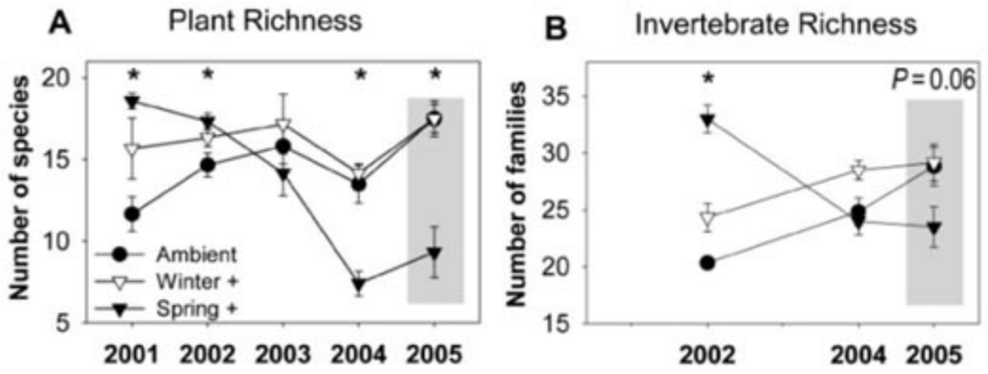

Fig. 3. Watering treatment effects on (**A**) plant species richness and (**B**) invertebrate family richness. Data represent treatment means ± 1 SE. Gray shading highlights the year that late natural rainfall mirrored the spring-addition watering treatment. See tables S2 and S3 for taxonomic listings of plant species and invertebrate families, respectively.

examined treatment effects on plant production and species composition over 5 consecutive years and quantified responses of invertebrate herbivores and their natural enemies over 3 years (*23*).

Effects of increased rainfall depended critically on the seasonality of the increase. Supplemental water addition during the wet winter period produced moderate increases in plant production in some years of the study (Fig. 2), but effects did not extend to higher trophic levels (Figs. 3 and 4). In general, communities in winter-addition and ambient rainfall plots responded similarly across years to annual variation in rainfall.

Extending the rainy season via spring water addition produced much more dramatic changes in the grassland community. Plant production more than tripled in the first year and more than doubled in the second compared with the control (Fig. 2A). The strongest initial response was by nitrogen-fixing forbs, whose production increased by nearly two orders of magnitude with extended spring rainfall (Fig. 2B). Exotic annual grasses showed a weaker response to the first year of spring water addition, but after the proliferation of nitrogen-fixing forbs that year, annual grass production rose dramatically (Fig. 2C). These grasses, so-called winter annuals because they are the first plants to germinate each year and are among the earliest to complete their life cycle and senesce, generally do not respond to extensions of the rainy season beyond April (*22*, *24*). Early phenology thus limited the direct response of annual grasses to extended rainfall but allowed these plants to benefit in the subsequent growing season from a fertilization effect after decomposition of abundant N-fixer litter (*25*–*27*). As this process was repeated year after year, the accumulation of annual grass litter suppressed germination and regrowth of leafy forbs (Fig. 2D), as has often been seen in California annual grasslands (*26*, *28*–*30*), and drove steep declines in plant species richness (Fig. 3A).

Shifts in plant composition in spring-addition plots had important consequences for biodiversity and food web structure. Initially, extended rainfall promoted increased plant species richness (Fig. 3A), and this increase, coupled with greater primary production and water availability, supported greater diversity and abundance of invertebrate herbivores, predators, and parasitoids (Figs. 3B and 4). As forbs were eliminated from spring-addition plots by annual grasses, however, plant species richness collapsed to nearly half that in control plots. With early-senescing annual grasses increasingly dominating the resource base, food availability and habitat quality for higher trophic levels diminished. This was especially true during summer, when late-blooming forbs provide a critical food resource for invertebrate herbivores (fig. S2). In contrast, annual grass litter has low nutritional value, and monocultures of these plants offer less structural complexity than mixed grass-forb assemblages.

By the fifth year of the study, when heavy rains continued into summer in a naturally extended rainy season throughout northern California, spring-addition plots stood out as islands of low biodiversity and reduced consumer abundances (Fig. 3B and 4). In addition to the nearly 50% reduction in plant species richness in spring-addition relative to control plots, invertebrate richness was 20% lower, and herbivore and predator abundances were each nearly 50% lower than ambient values measured in control plots. This simplification of the grassland community did not result from climatic conditions that were inherently unfavorable to production and diversity. Species at every trophic level benefited strongly from experimental extension of the rainy season in spring-addition plots early in the study, just as they did from a natural extension of the rainy season in winter-addition and control plots late in the study. But as altered environmental conditions persisted across years, individualistic responses by species to climate were overshadowed by the lagged effects of altered community-level interactions. The congruence between initial responses to artificial extension in spring-addition plots and responses in the grassland as a whole to naturally late rainfall in year 5 provides compelling evidence that these mechanisms are real rather than experimental artifacts.

Uncertainty remains in the projections of global climate models; indeed, the next-generation Hadley model (HadCM3) forecasts decreased rainfall over much of California (*31*). Yet under any scenario of future climate change, prediction of ecological effects will require understanding the web of interactions that mediate species- through ecosystem-level responses (*14*). To date, forecasts of range shifts and extinction probabilities are based largely on species-climate envelope models (*32*–*34*). These models are powerful initial tools

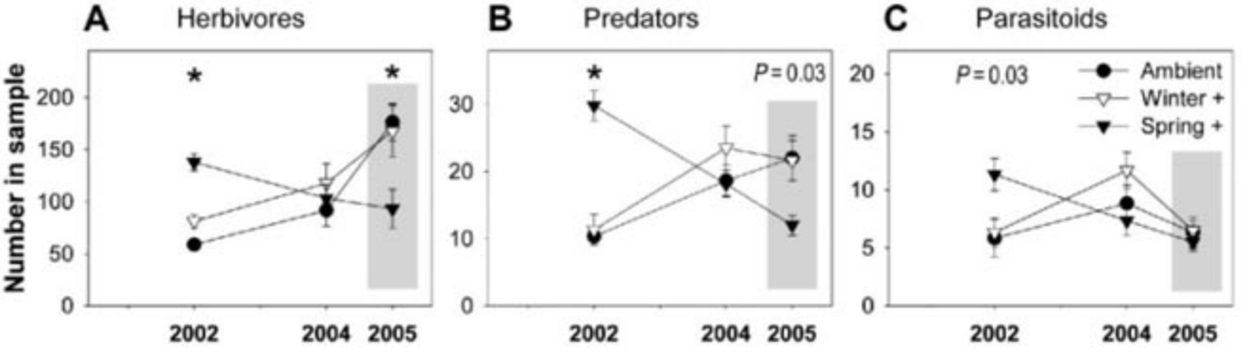

Fig. 4. Watering treatment effects on abundances (mean ± SE) of (**A**) invertebrate herbivores, (**B**) predators, and (**C**) parasitoids, as measured in sweep net and pitfall trap collections. Gray shading highlights responses in the final year of the study, when late natural rainfall mirrored the spring-addition watering treatment.

with which to explore consequences of alternative climate scenarios, but they cannot forecast lagged impacts of altered higher-order interactions that will govern the trajectories of ecosystems under sustained climatic change. Nonlinearities are expected from the assembly of new combinations of species brought together by climate-induced range shifts, but these can also arise from environmental effects on the strength and direction of interspecific interactions without any change in species composition (*35*, *36*). The nature and scales of these effects are best revealed by long-term experiments in natural field settings that improve understanding of how climate change impacts propagate through ecological communities. Indirect effects of climate on species will commonly lag behind direct effects, but their importance makes system-level interactions crucial to climate change forecasting even at subdecadal time scales.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/640/DC1
Materials and Methods
Figs. S1 and S2
Tables S1 to S3

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An X Chromosome Gene, *WTX*, Is Commonly Inactivated in Wilms Tumor

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Wilms tumor is a pediatric kidney cancer associated with inactivation of the *WT1* tumor-suppressor gene in 5 to 10% of cases. Using a high-resolution screen for DNA copy-number alterations in Wilms tumor, we identified somatic deletions targeting a previously uncharacterized gene on the X chromosome. This gene, which we call *WTX*, is inactivated in approximately one-third of Wilms tumors (15 of 51 tumors). Tumors with mutations in *WTX* lack *WT1* mutations, and both genes share a restricted temporal and spatial expression pattern in normal renal precursors. In contrast to biallelic inactivation of autosomal tumor-suppressor genes, *WTX* is inactivated by a monoallelic "single-hit" event targeting the single X chromosome in tumors from males and the active X chromosome in tumors from females.

Wilms tumor (nephroblastoma) is the most common pediatric kidney cancer and is derived from pluripotent renal precursors that produce undifferentiated blastemal cells, primitive epithelial structures, and stromal components [reviewed in (*1*)]. In 1972, Knudson and Strong proposed that Wilms tumor, like retinoblastoma, may develop as a consequence of two independent rate-limiting genetic events, subsequently defined as biallelic

inactivation of a tumor-suppressor gene (*1*). This prediction was borne out by the identification of *WT1*, a zinc finger transcription factor gene on chromosome 11p13 that is targeted by germline heterozygous deletions in the WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation), by germline point mutations in the Denys-Drash syndrome (Wilms tumor, pseudohermaphroditism, and nephropathy), and by somatic biallelic inactivation in 5 to 10% of sporadic Wilms tumors (*2*–*4*). Although inactivation of *WT1* affects only a small subset of cases, this gene has been shown to encode a master regulator of kidney development, which appears to be required for the survival and subsequent differentiation of renal stem cells (*5*, *6*). Other known abnormalities in Wilms tumor include activating mutations in the β-catenin gene (*CTNNB1*) on chromosome 3p22, which often coincide with *WT1* mutations (*7*), and epigenetic dysregulation of *IGF2* and *H19* (*8*) at the Beckwith-Wiedemann syndrome locus on chromosome 11p15. In the majority of cases, however, no specific genetic abnormalities have been identified.

To search for genetic abnormalities in sporadic Wilms tumor, we performed a detailed genome-wide scan (70-kb median resolution) for DNA copy-number changes in 51 primary tumor specimens using long-oligonucleotide array comparative genomic hybridization (array CGH) (*9*). In marked contrast to most adult epithelial cancers, the baseline CGH profile in Wilms tumor was quite stable, with an average of only 3.1 large (more than 5 mb) DNA copy-number changes per tumor after accounting for known copy-number polymorphisms (*10*, *11*). As expected, we detected single-copy losses in a subset of cases, including known loci of loss of heterozygosity (LOH) at chromosomes 1p (18%), 16q (14%), 11p (6%), and 7p (4%) (*4*, *12*). LOH at chromosome 11p15 is commonly associated with gene conversion rather than single-copy loss and is therefore underrepresented in our array CGH analysis (*13*). Notably, we detected small overlapping deletions at chromosome locus Xq11.1 in tumors from 5 out of 26 male patients. The deletions involved only one to three probes in each case, with a minimal area of overlap implicating a single previously uncharacterized gene (*FAM123B*/*FLJ39827*) that we named *WTX*, for "Wilms Tumor gene on the X chromosome" (Fig. 1, A and B). All deletions were confirmed by quantitative polymerase chain reaction (qPCR) of genomic DNA, including two cases with deletion breakpoints internal to *WTX* (Fig. 1C). Genomic deletions were also analyzed by fluorescence in situ hybridization (FISH) (representative example in Fig. 1D).

The endogenous *WTX* transcript differed from that predicted by database annotation in the 3′ end and required assembly with the use of rapid amplification of cDNA ends and reverse transcriptase (RT)–PCR from human and mouse cDNA (fig. S1). The full-length transcript (7.5 kb) encodes a protein of 1135 amino acids, containing a nuclear localization signal, two coiled-coil domains, an acidic domain that overlaps the first coiled coil, and a proline-rich domain (Fig. 2A). *WTX* orthologs are present in vertebrates, including zebrafish, but do not share substantial homology with other genes of known function (fig. S2).

To search for intragenic point mutations, we sequenced the entire coding region of *WTX* in 82 Wilms tumor specimens, including the 51 cases previously analyzed by array CGH. Intragenic truncating mutations were identified in six tumors, including one nonsense mutation (Arg^{358}→Ter, where Ter is the termination of the chain) observed in two independent cases (table S1). All predicted protein truncations were N terminal to the second coiled-coil domain encoded by *WTX* (Fig. 2A). A seventh case harbored a missense mutation (Lys^{292}→Asn^{292}) affecting an evolutionarily conserved residue. Consistent with somatic events, *WTX* mutations were absent in matched normal tissue in all four cases where such tissue was available (Fig. 2B) (table S1). Mutations identified in cases without matched normal tissue were not detected in control DNA from 269 healthy individuals.

In contrast to the classical biallelic "two-hit" Knudson model, the identification of somatic mutations affecting an X chromosome gene in sporadic Wilms tumor raises the possibility of "one-hit" inactivation of a tumor-suppressor gene. This applies to the hemizygous deletions and point mutations detected in males and, given that *WTX* is located in a chromosomal region

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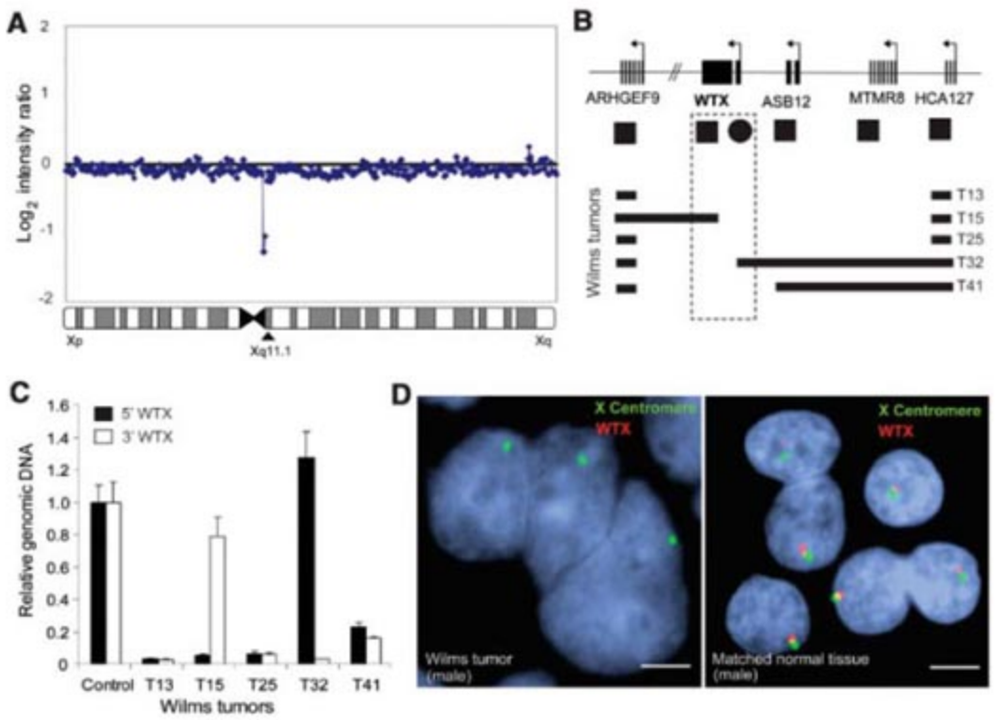

Fig. 1. Identification of *WTX* deletions in Wilms tumor. (**A**) Array CGH profile for a representative *WTX* deletion in Xq11.1 in a male patient. All probes on the X chromosome are shown. (**B**) Minimal region of overlap for deletions targeting *WTX*. Genes flanking *WTX* (arrows depict the direction of transcription), array CGH probes (squares), and a confirmatory qPCR marker (circle) are shown. The boundaries of deletions detected in five male Wilms tumor cases define a minimal region of overlap centered on *WTX* (box). (**C**) Quantitative PCR of genomic DNA from five male Wilms tumors and one normal male kidney control, with the use of primers for the 5′ and 3′ ends of *WTX*. Tumors T13, T25, and T41 show complete absence of *WTX*, whereas tumor T15 lacks only the 5′ end and tumor T32 lacks only the 3′ end of the gene. Error bars indicate standard deviation. (**D**) FISH analysis demonstrating a somatic deletion in a male Wilms tumor (case 13) with the use of a probe for *WTX* (red) and a probe for the X chromosome centromere (green) as a control. The tumor lacks the red *WTX* signal, whereas both signals are present in matched normal tissue. Scale bars, 5 μm.

subject to X inactivation (*14*), it would also apply to the heterozygous mutations detected in females if the active copy of the X chromosome is selectively targeted. To test this hypothesis, we used FISH analysis to search for heterozygous *WTX* deletions in female cases and to determine whether they affected the active or inactive X chromosome. Heterozygous *WTX* deletions in female cases were more reliably identified by FISH, compared with the initial array CGH analysis, presumably because of high signal-to-noise ratios for single-copy changes involving a small number of probes. Indeed, among 25 female Wilms tumor cases analyzed, 6 showed deletion of one *WTX* allele, as assessed by FISH with a probe for *WTX* and control probes for the X chromosome centromere and a telomeric Xq locus (table S1) (fig. S3). To determine whether these deletions targeted the active X chromosome allele, we performed simultaneous FISH analysis for *WTX*, the X chromosome centromere, and the inactive X chromosome coating transcript *Xist* (*15*). In all four cases tested, the intact *WTX* gene was present in the inactive X chromosome coated by *Xist*, whereas no *WTX* signal was detected in the active X chromosome that lacked *Xist* hybridization (Fig. 2C). Heterozygous *WTX* deletions in female Wilms tumors therefore target the active X chromosome, leading to gene inactivation by a single event.

We extended this analysis to an intragenic mutation of *WTX* (Glu^{334}→Ter) in a female Wilms tumor in which it was possible to compare the nucleotide sequence of PCR products generated from genomic DNA or cDNA. Indeed, although the mutation was heterozygous in genomic DNA, only the mutant sequence was detected in the tumor-derived transcripts, consistent with monoallelic expression of the mutant copy from the active X chromosome (Fig. 2D). Taken together with the FISH analysis, these data indicate that intragenic mutations and gross chromosomal deletions of *WTX* occur at comparable frequencies in male and female Wilms tumor cases and that in females they exclusively target the active X chromosome.

Overall, of 51 tumors tested for both gene-copy alterations and intragenic mutations, 11 (21.6%) had *WTX* deletions, and 4 (7.8%) had point mutations (total 15 out of 51, 29.4%) (table S1). In these tumors, *WT1* mutations were detected in three cases (5.9%) and β-catenin mutations in four cases (7.8%). As expected (*7*), there was overlap between *WT1* and β-catenin mutations (two out of three cases with *WT1* mutations). In contrast, no tumor with a deletion or point mutation in *WTX* contained mutations in *WT1* or β-catenin (Fig. 2E). Whether inactivation of WTX defines a distinct subset of nephroblastomas remains to be investigated.

In contrast to other tumor-suppressor genes, *WT1* has a developmentally regulated pattern of expression in the organ in which the tumor arises. The restricted expression of *WT1* in renal blastemal stem cells and glomerular podocyte precursors is consistent with the presumed cell type of origin of Wilms tumor and highlights the key physiological role of *WT1* in normal kidney development (*16*). In the mouse, *WTX* expression is relatively high in the neonatal brain and kidney and then declines substantially in the mature organs (Fig. 3A). Lung and spleen also express *WTX*, but with a less notable developmental profile. The temporal patterns of *WTX* and *WT1* expression within the kidney are virtually identical, consistent with a wave of differentiation that is ongoing at the time of birth and is completed by postnatal week 3 (Fig. 3B). As assessed by RNA in situ hybridization, *WT1* and *WTX* display a high, but not complete, degree of overlap in expression in the kidney. Similar to *WT1*, *WTX* is expressed in the condensing metanephric mesenchyme and in early epithelial structures that are precursors to glomeruli

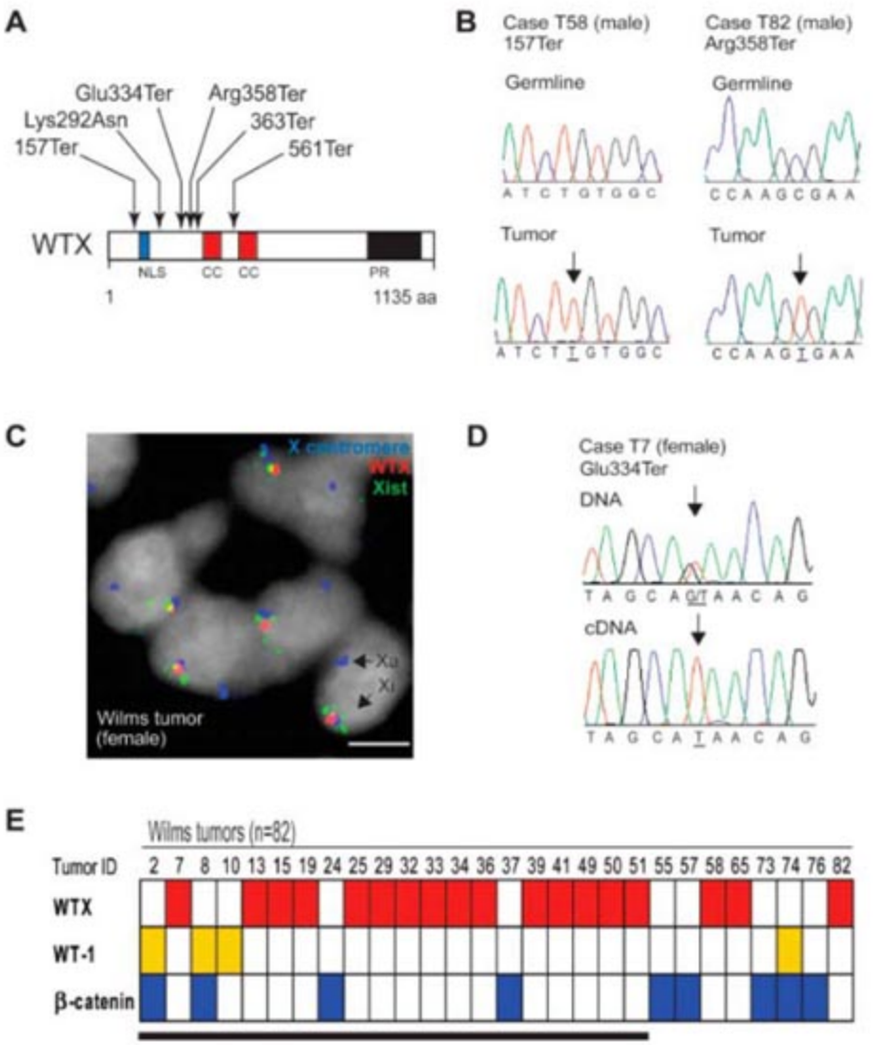

Fig. 2. Analysis of *WTX* mutations in Wilms tumor. (**A**) Schematic representation of *WTX* and potential functional domains, including the nuclear localization signal (NLS), the two coiled-coil domains (CC), and the proline-rich domain (PR). The relative positions of all point mutations are shown. aa, amino acids. (**B**) Representative nucleotide sequence tracings of a frame shift (left) and a nonsense mutation (right) of *WTX* in male Wilms tumors and matching germline tissue. Arrows indicate the position of the two hemizygous mutations, 439 insertion T leading to 157Ter and a substitution of T for C at position 1072, leading to Arg^{358}→Ter. (**C**) Representative FISH analysis of a Wilms tumor from a female patient showing a deletion of the *WTX* allele on the active X chromosome. Probes for the X centromere (blue), *WTX* (red), and *Xist* (green) were used. Only one copy of *WTX* is present, associated with the inactive (*Xist* positive) X chromosome (Xi). The active X chromosome (Xa) is marked by the X centromere probe but lacks both *WTX* and *Xist*. The same pattern was observed in all tumor cells, consistent with tumor clonality. Scale bar, 5 μm. (**D**) Sequence tracings of genomic DNA and cDNA from a female Wilms tumor case with a heterozygous *WTX* mutation. Both alleles are detectable in genomic DNA but only the mutant allele is present in cDNA, indicating that only the mutant *WTX* allele is transcribed. (**E**) Schematic representation of Wilms tumor cases with mutations in WTX (red), WT1 (yellow), or β-catenin (blue). Although WT1 and β-catenin mutations can be present in the same tumor, there is no overlap between mutations in WTX and mutations in these two genes. WTX mutations are listed in table S1. WT1 and β-catenin mutations are listed in table S2. Tumors 1 through 51 (underlined) were tested for both deletions and point mutations in WTX. The remaining tumors were tested for point mutations only.

(Fig. 3, C and D). Thus, both genes are present in the pluripotent cells that are the presumed precursors of Wilms tumor.

Functional studies of *WT1* and other genes implicated in Wilms tumorigenesis have been hampered by the absence of either mouse tumor models or experimentally manipulable Wilms tumor cell lines. Thus, we ectopically expressed *WTX* in cancer cell lines that have been used to model *WT1* function. In human embryonic kidney (HEK) 293 cells and in U2OS human osteosarcoma cells, transfection of *WTX* led to a marked suppression of colony formation (Fig. 3E). Apoptosis was evident in HEK-293 cells 48 hours after ectopic expression of *WTX* (fig. S4). Studies in such heterologous cell types point to functional properties consistent with a tumor suppressor, but a more complete understanding of protein function will require in vivo studies of this developmentally regulated gene in the appropriate cellular context (*5*, *6*).

Our data suggest that *WTX* is a Wilms tumor–suppressor gene with a potentially important role in normal kidney development. In addition, the localization of *WTX* on the X chromosome allows for complete inactivation by one mutational event targeting the single X allele in males or the active X allele in females. X-linked familial syndromes with increased cancer risk (*17*–*19*) preferentially affect males. In contrast, *WTX* is frequently altered in sporadic tumors by a single somatic event that affects both sexes equally. One-hit inactivation of a tumor-suppressor gene on the X chromosome is a departure from the traditional biallelic Knudson model and has been postulated but never documented (*20*, *21*). Although single-hit gene inactivation in Wilms tumor could lead to greatly increased tumorigenesis, its restriction to a limited pool of pluripotent target cells within a specific developmental window would mitigate this effect. As for *WTX*, high-resolution copy-number analysis and direct sequencing may be required for the identification of other X chromosome tumor suppressors subject to monoallelic inactivation, given that they are not marked by the characteristic secondary allelic loss (LOH) traditionally used for mapping. Together with recently described X chromosome abnormalities in a subset of breast cancer (*22*), the frequency of single-hit gene inactivation exemplified by *WTX* suggests that X chromosome genes may play unappreciated roles in human cancer.

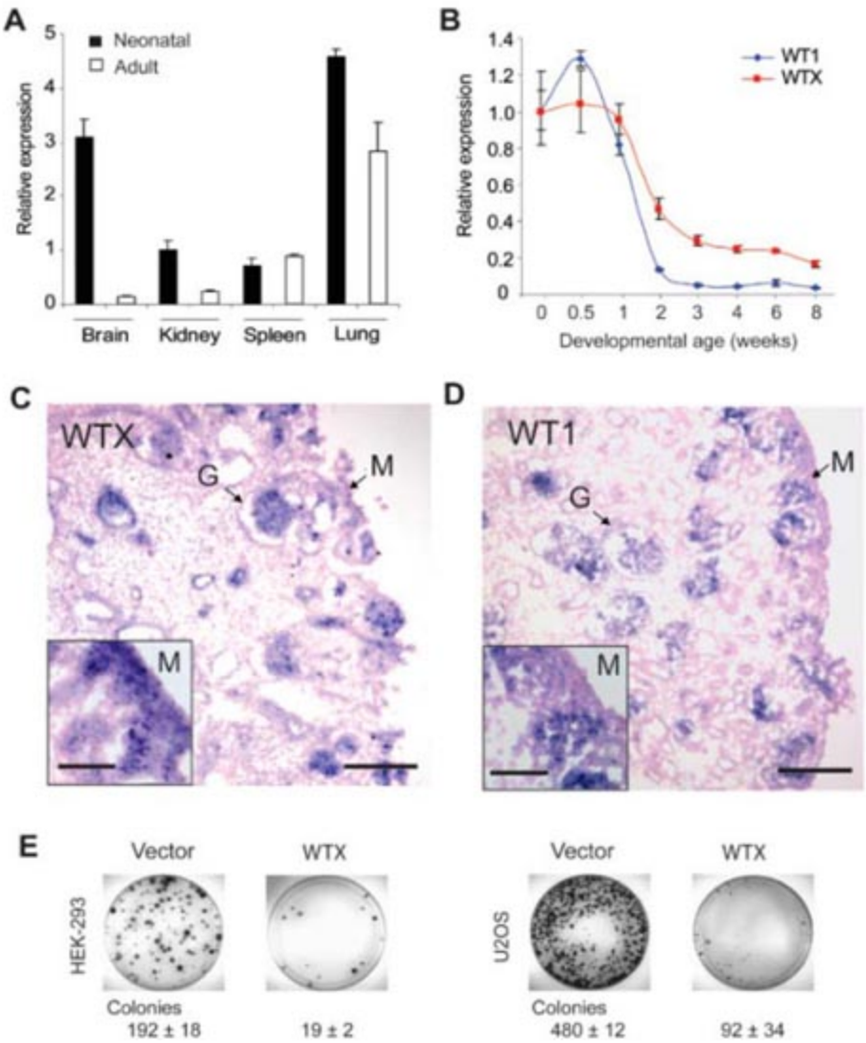

Fig. 3. Regulated expression of *WTX*. (**A**) qPCR quantitation of *WTX* mRNA in mouse neonatal and adult tissues. (**B**) Comparison of the developmental time course of *WT1* and *WTX* expression in mouse postnatal kidneys. In (A) and (B), expression levels were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and displayed relative to neonatal kidneys. Error bars indicate standard deviation. (**C** and **D**) RNA in situ hybridization of human embryonic kidneys (week 13) showing similar but not identical expression patterns of *WTX* and *WT1*. Condensing metanephric mesenchyme (M) and glomerular precursors (G) are indicated. Scale bars, 250 μm. Insets are higher-magnification images of the mesenchyme (M). Scale bars, 100 μm. (**E**) Suppression of colony formation after ectopic expression of *WTX* in HEK-293 cells and U2OS cells. Cells were cotransfected with a WTX expression plasmid (or empty vector) and a plasmid encoding a drug-resistance marker (puromycin). Experiments were performed in triplicate and drug-resistant colonies were stained after 2 weeks. Representative plates and mean colony numbers are shown (± standard error of the mean).

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The DEAD-Box RNA Helicase Dbp5 Functions in Translation Termination

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In eukaryotes, termination of messenger RNA (mRNA) translation is mediated by the release factors eRF1 and eRF3. Using *Saccharomyces cerevisiae* as a model organism, we have identified a member of the DEAD-box protein (DBP) family, the DEAD-box RNA helicase and mRNA export factor Dbp5, as a player in translation termination. Dbp5 interacts genetically with both release factors and the polyadenlyate-binding protein Pab1. A physical interaction was specifically detected with eRF1. Moreover, we show that the helicase activity of Dbp5 is required for efficient stop-codon recognition, and intact Dbp5 is essential for recruitment of eRF3 into termination complexes. Therefore, Dbp5 controls the eRF3-eRF1 interaction and thus eRF3-mediated downstream events.

DEAD-box RNA helicases are found in almost all organisms and function in many fundamental steps in the life of RNA molecules, ranging from transcription to decay. They use the energy from adenosine triphosphate hydrolysis to rearrange RNA structures or to dissociate RNA/protein complexes (*1*). The DEAD-box helicase Dbp5 shuttles between the nucleus and the cytoplasm and is involved in translocation of the mature mRNA/protein complex into the cytoplasm (*2*). Consistently, Dbp5 is localized to the nuclear rim, where it interacts with components of the nuclear pore complex (NPC) (*2*, *3*). Dbp5 is also distributed within the cytoplasm of yeast, higher eukaryotes, and human cells, but a cytoplasmic function has not yet been defined (*4*–*6*).

To get insights into its cytoplasmic function, we used *Saccharomyces cerevisiae* to investigate whether Dbp5 associates with mRNAs during translation. Western blot analysis of sucrose density fractionation experiments revealed that, like the polyadenylate-binding protein Pab1, significant amounts of the extracted Dbp5 (~60%, which equals ~40% of the total Dbp5) but not of Gfd1 (a nuclear pore–associated factor) were detectable in polysome-containing fractions (Fig. 1, A and B). The addition of puromycin, which specifically disrupts polysomes, confirmed that Dbp5 co-sediments with polyribosome-containing mRNAs (fig. S1). A potential role of Dbp5 in translation is supported by the finding that *dbp5/rat8* mutants are hypersensitive to translational inhibitors (Fig. 1C). This effect is not due to defects in mRNA export, because *rat7-1*, which in contrast to *dbp5* displays strong mRNA export defects even at 25°C (Fig. 1D), is not hypersensitive to those inhibitors.

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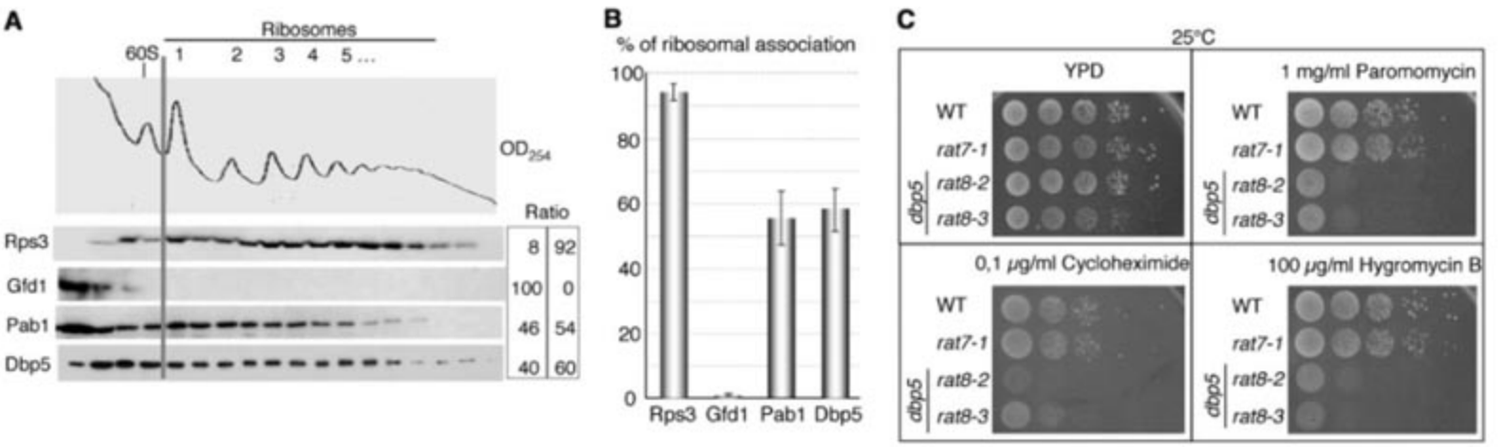
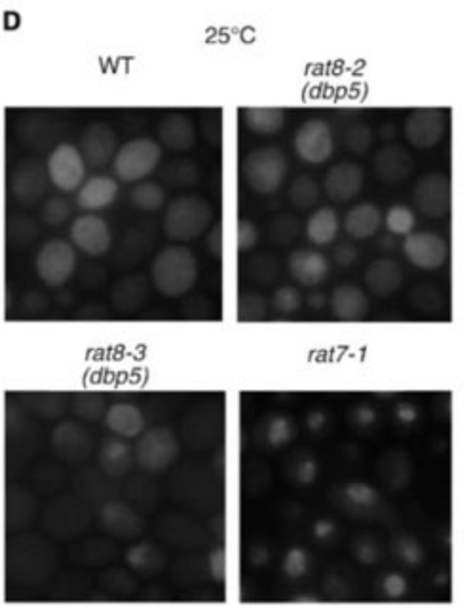


Fig. 1. Dbp5 associates with polysomes during translation, and mutants are hypersensitive to translational inhibitors. (**A**) Supernatants of cell extracts of log-phase wild-type cells, expressing functionally green fluorescent protein (GFP)–tagged versions of *GFD1*, *DBP5*, or *PAB1*, were fractionated through 15 to 50% sucrose gradients and subjected to Western blot analysis. Antibodies to Rps3 detected endogenous ribosomal protein. Absorbance at 254 nm (OD, optical density) shows the distribution of ribosomes. The ratio of the extracted proteins is shown as follows: amount of the unbound proteins (left) or mono- and polysome-bound proteins (right). (**B**) Quantification of at least three independent experiments shown in (A). (**C**) Growth of wild-type (WT), *rat7-1*, *rat8-2*, and *rat8-3* strains on yeast extract, peptone, and dextrose (YPD) medium with and without translational inhibitors in 10-fold serial dilutions of similar cell numbers. (**D**) mRNA localization in log-phase wild-type, *rat7-1*, and *rat8* mutants at 25°C.



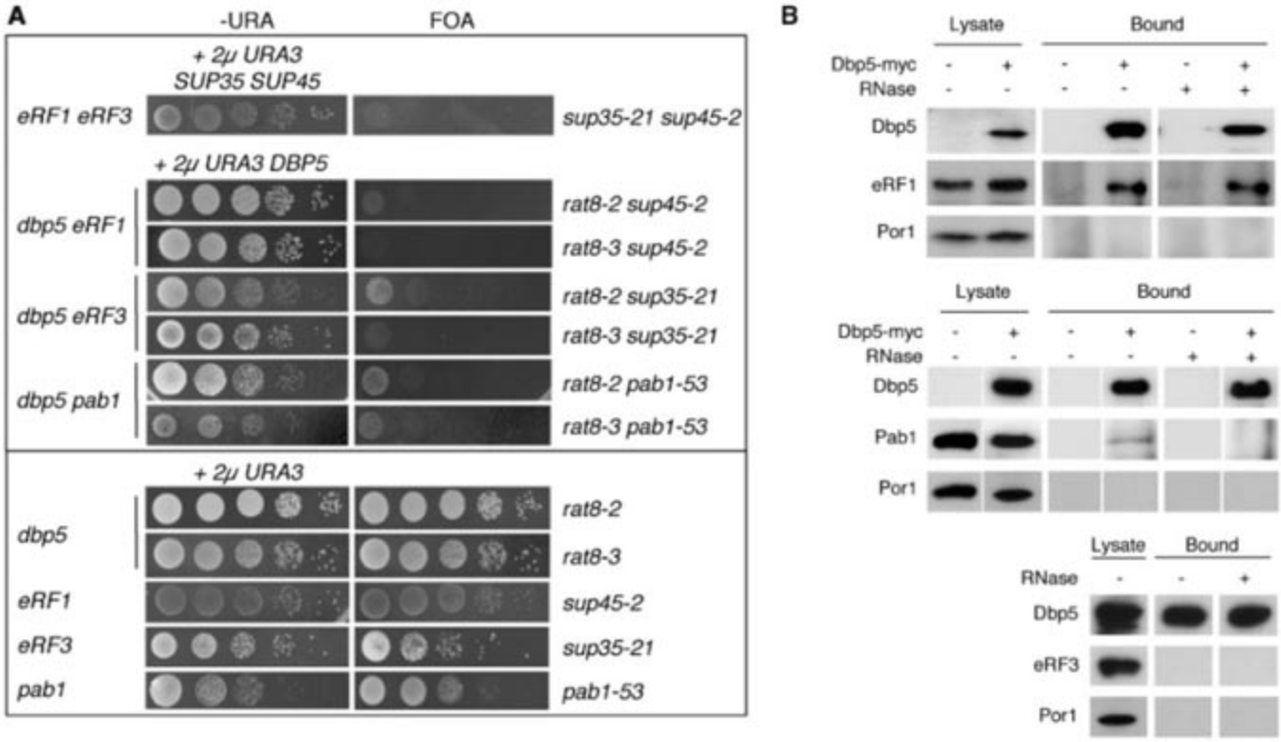


Fig. 2. Genetic and physical interaction of Dbp5/Rat8 with translation termination factors. (**A**) Growth of all indicated double mutants carrying a 2μ *URA3* vector encoding either *DBP5* or *SUP35 SUP45* and all single mutants carrying an empty vector was analyzed on −URA- and 5′-fluoroorotic acid (FOA)–containing plates that select for the loss of plasmid. (**B**) Immunoprecipitation of functionally tagged versions [or the endogenous release factors (see fig. S3)] of eRF1 (Sup45-GFP), eRF3 (Sup35-GFP), and Pab1-GFP with Myc-tagged Dbp5. Total lysates were split and incubated with or without RNase, and Dbp5-bound proteins were detected on Western blots with an antibody to GFP. Endogenous Por1 served as a negative control.

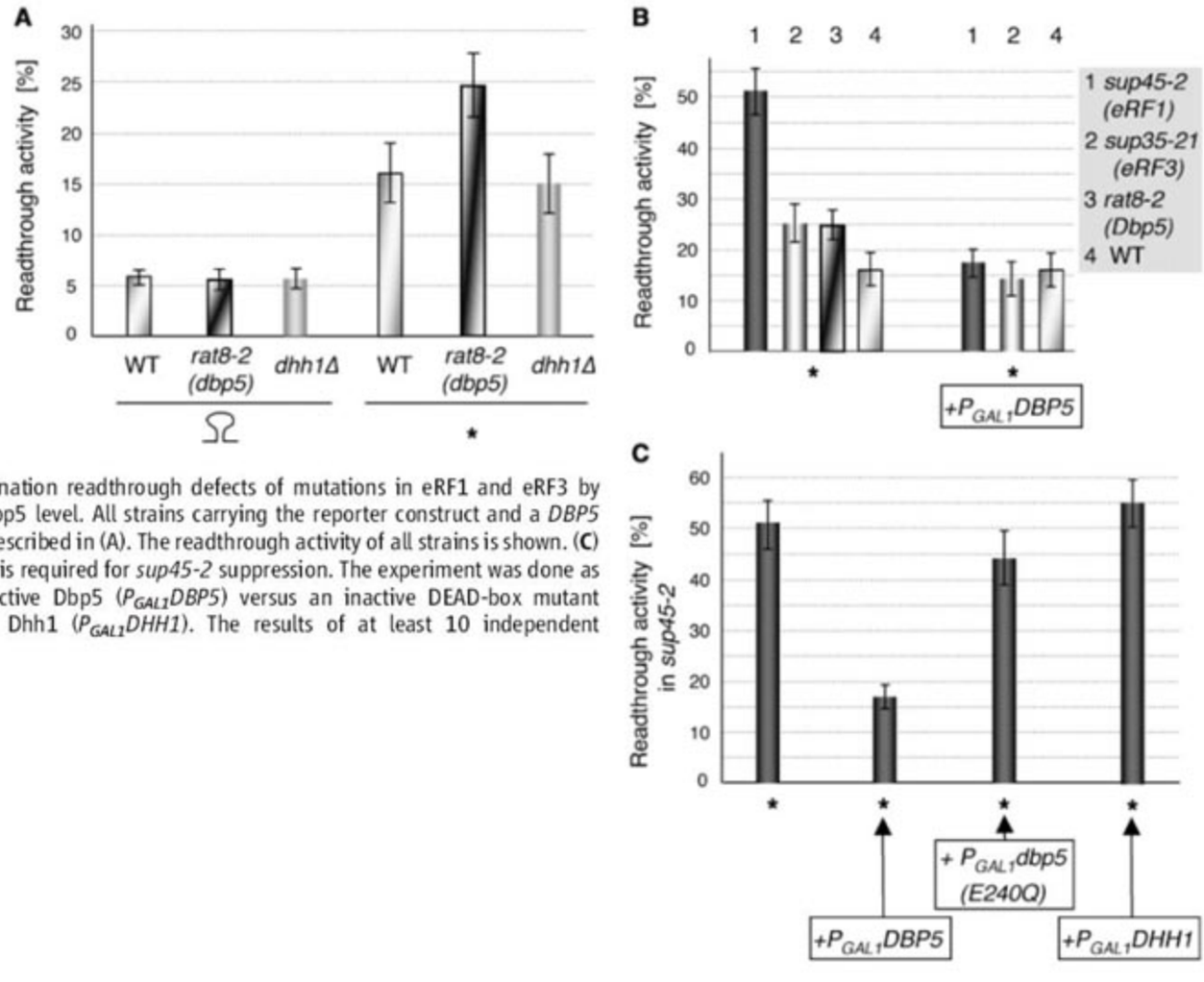


Fig. 3. Dbp5 is required for efficient stop codon recognition. (**A**) Readthrough activities in wild-type, *rat8-2*, and *dhh1Δ* are shown. All strains carrying either of the reporter constructs were grown to log phase and shifted to 37°C for 15 min before cell lysis. β-galactosidase and luciferase activities were measured and their ratios were used to calculate the relative molar luciferase expression. (**B**) Suppression of the termination readthrough defects of mutations in eRF1 and eRF3 by increased ($P_{GAL1}DBP5$) Dbp5 level. All strains carrying the reporter construct and a *DBP5* plasmid were treated as described in (A). The readthrough activity of all strains is shown. (**C**) Catalysis activity of Dbp5 is required for *sup45-2* suppression. The experiment was done as described in (B), with active Dbp5 ($P_{GAL1}DBP5$) versus an inactive DEAD-box mutant ($P_{GAL1}dbp5\ E240Q$) and Dhh1 ($P_{GAL1}DHH1$). The results of at least 10 independent experiments are shown.

Different genetic approaches were carried out to investigate in which phase of translation Dbp5 might be acting. Dbp5 overexpression studies revealed that mutations in genes encoding initiation or elongation factors were not suppressed by high-copy *DBP5*, whereas mutations in both of the eukaryotic release factors eRF1 (*SUP45*) and eRF3 (*SUP35*), as well as a mutation in Pab1, were specifically suppressed (fig. S2). Moreover, similarly to the synthetic lethal effect seen when both release-factor mutants (*sup35-21* and *sup45-2*) are combined, *dbp5/rat8* mutants are synthetically lethal with mutant eRF1, and the growth of *dbp5/rat8* mutants is severely inhibited when combined with mutant eRF3 or Pab1 (*pab1-53*) (Fig. 2A), indicating a potential function of Dbp5 in translation termination.

Translation termination is mediated by recognition of a stop codon via the transfer RNA (tRNA)–mimicking protein eRF1 and subsequent hydrolysis of the ester bond connecting the polypeptide chain and the tRNA, stimulated by the guanosine triphosphatase activity of eRF3. Although eRF3 is unable to promote in vitro termination on its own, it enhances eRF1 activity (*7*). Direct interactions between Pab1 and eRF3 have been described in yeast, frog, and mammalian cells (*7*, *8*), and overexpression of *PAB1* in yeast suppresses effects associated with mutant eRF3 in vivo, suggesting a functionally important interaction of these proteins for termination (*9*), possibly as bridging factors to channel the terminating ribosomes back to the 5′ end of an mRNA (*8*). To get insights into how Dbp5 might contact the termination machinery, we performed coimmunoprecipitation experiments that revealed a stable interaction between Dbp5 and eRF1 (Fig. 2B and fig. S3B). In contrast, no interaction between Dbp5 and eRF3 was found, whereas an interaction between Pab1 and Dbp5 was ribonuclease (RNase)–sensitive, indicating concurrent binding of Dbp5 and Pab1 to the same mRNA but no simultaneous presence of Dbp5 and eRF3.

To demonstrate an active role of Dbp5 in translation termination, we assayed the stop codon recognition under different conditions. First, we showed that like eRF1 and eRF3 mutants, *dbp5/rat8* mutant cells show increased termination readthrough activity in luciferase dual-reporter assays (Fig. 3). The assay is based on compared expression of β-galactosidase and luciferase open reading frames, separated by a stem loop or a stop codon (fig. S4A), which allows us to compare the frequency of translational readthrough in different strain backgrounds (*10*). In agreement with previous results, we found a basal readthrough activity of ~15 to 17% in wild-type cells (*10*). Although mutant *dbp5* did not influence readthrough activities in the presence of the stem loop, Dbp5 was clearly required for efficient recognition of the termination codon, in contrast to Dhh1 (Fig. 3A). Dhh1 is another DEAD-box RNA helicase family member, which has been implicated in connecting translation to mRNA degradation, because it can act as a translational repressor and an activator of mRNA decapping (*11*). However, in contrast to *dbp5* (Fig. 2A), no genetic interaction between *dhh1Δ* and any of the termination-factor mutants was detected (fig. S4C). The rate of readthrough in *dbp5* mutant cells was very similar to that seen with a mutation in eRF3 (Fig. 3B). The termination readthrough defects in eRF1 and eRF3 mutants were fully suppressed in the presence of high-copy Dbp5 but not Dhh1 (Fig. 3, B and C). This was confirmed in a different assay, in which the decreased translational fidelity of either defective release factor, reflected by decreased growth rates in the presence of paromomycin, was efficiently suppressed by high-copy *DBP5* (fig. S4B). Moreover, catalytic RNA helicase activity of Dbp5 is required for this suppression, because a mutation in its DEAD-box (Glu^{240}→Gln^{240}) prevented suppression (Fig. 3C).

Besides functioning as an eRF1-stimulating protein, eRF3 is a key mediator that transmits the termination signal to mRNA decay (*7*). The RNA helicase Upf1 (human RENT1 or HUPF1) is involved in the nonsense-mediated decay (NMD) of aberrant mRNAs, and deletion of *UPF1* leads to an increased termination readthrough (*12*). Although Upf1 and its interacting proteins Upf2 and Upf3 are capable of binding to eRF3, it is hypothesized that Pab1 competes for this interaction and thereby precludes the binding and destabilizing activities of these NMD factors at normal terminators, supporting a role for Upf1 in coupling premature termination events to NMD rather than a function in regular translation (*12*). To investigate a potential involvement of Dbp5 in NMD, we tested whether mutations in *DBP5* stabilize NMD substrates and found that this is not the case, in contrast to *upf1Δ* (fig. S5A). Also, neither genetic interactions between *dbp5* mutants and *upf1*, *upf2*, or *upf3* deletion strains, nor genetic interactions between *upf1Δ* and either eRF1 or eRF3 mutants, were detectable (fig. S5, B and C), in contrast to the synthetic growth defects detected be-

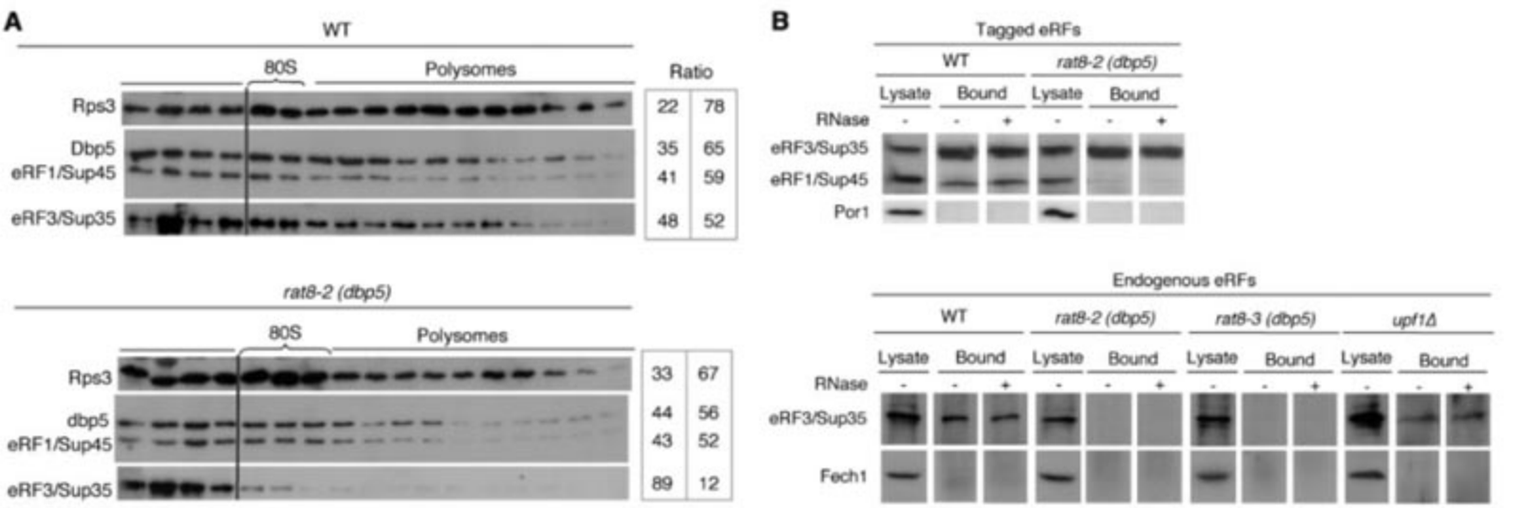


Fig. 4. Active Dbp5 is required for the incorporation of eRF3 into translation termination complexes. (**A**) Sucrose fractionation experiments (with 15 to 50% sucrose gradients) of log-phase wild-type and *rat8-2* strains shifted to 37°C for 20 min were performed, and Western blot detection of TAP-tagged *SUP35*, *SUP45*, and *GFP-DBP5* or *GFP-rat8-2*, respectively, and Rps3 is shown in wild-type (upper panel) and *rat8-2* (lower panel) cells. The ratio of the extracted proteins is shown as follows: amount of the unbound proteins (left) or mono- and polysome-bound proteins (right). (**B**) Top: Sup35-TAP purification from log-phase wild-type and *rat8-2* cells expressing *SUP45-GFP* shifted to 37°C for 20 min prior to lysis is shown as total lysates and purified proteins (bound) after incubation with protein A for 3 hours with or without RNase. Sup45-GFP and Por1 (negative control) were detected with antibodies to GFP and Por1, respectively. Bottom: Immunoprecipitations of endogenous eRF1 from wild-type, *upf1Δ*, *rat8-2*, and *rat8-3* cells treated as described above are shown. The presence of endogenous eRF3 and Fech1 (negative control) is shown.

tween *dbp5/rat8* and either release-factor mutant (Fig. 2A). Further, the readthrough defects of *dbp5/rat8* and either *upf* mutant are not additive (fig. S5D). Together, these findings suggest a general function for Dbp5 in translation termination and support an exclusive function for Upf1 on NMD substrates.

To gain mechanistic insights into the function of Dbp5 during translation termination, we compared polysomes of *rat8-2* to those of the wild-type and found that *rat8-2* is defective in the recruitment of eRF3 into termination complexes (Fig. 4A). In a wild-type strain, roughly 60% of extracted Dbp5, eRF1, and eRF3 is ribosome-associated. In contrast, eRF3 is almost absent from the ribosomal fractions (12%) in *rat8-2* cells at the nonpermissive temperature, whereas approximately 55% of both Dbp5 and eRF1 remained polysome-associated, indicating that intact Dbp5 is required for eRF3 entry into the termination complexes. The corresponding rRNA profiles revealed an elevated monosome peak in *rat8-2* cells (resulting in three monosome fractions in the Western blot) as compared to the wild-type (two fractions) or *rat7-1*, reflecting the influence of Dbp5 on translation (fig. S6). The defect of the *dbp5/rat8*-mutant in eRF3 recruitment was further confirmed by analysis of the interaction between eRF1 and eRF3 (*13*), which was completely lost in *dbp5/rat8* mutant cells, in contrast to wild-type or *upf1*Δ strains (Fig. 4B).

Together our data reveal a requirement for functional Dbp5 for the entry of eRF3 into termination complexes and support the following model. Once the ribosome has reached a termination codon, eRF1 is recruited to the mRNA, possibly by Dbp5. The RNA helicase activity of Dbp5 might remodel the mRNA/protein complex to allow proper eRF1 positioning on the stop codon and thus an efficient termination reaction. Subsequent dissociation of Dbp5 from eRF1 is followed by the entry of eRF3 into the complex, which promotes the release of the peptide chain and allows eRF3-mediated downstream events. Thus, Dbp5 is involved in translation termination through its interaction with eRF1, and it controls the subsequent eRF1-eRF3 interaction through its dissociation from eRF1.

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Supporting Online Material

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Yeast Rtt109 Promotes Genome Stability by Acetylating Histone H3 on Lysine 56

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Posttranslational modifications of the histone octamer play important roles in regulating responses to DNA damage. Here, we reveal that *Saccharomyces cerevisiae* Rtt109p promotes genome stability and resistance to DNA-damaging agents, and that it does this by functionally cooperating with the histone chaperone Asf1p to maintain normal chromatin structure. Furthermore, we show that, as for Asf1p, Rtt109p is required for histone H3 acetylation on lysine 56 (K56) in vivo. Moreover, we show that Rtt109p directly catalyzes this modification in vitro in a manner that is stimulated by Asf1p. These data establish Rtt109p as a member of a new class of histone acetyltransferases and show that its actions are critical for cell survival in the presence of DNA damage during S phase.

Regulation of retrotransposition (RTT) by the *Saccharomyces cerevisiae* Ty1 transposon is intimately linked to the DNA-damage response (DDR), as many proteins are known to play roles in both pathways (*1*). We therefore reasoned that uncharacterized *RTT* genes might represent novel DDR factors. Although *RTT109* has not been characterized in detail, it was previously linked to the DDR through genomewide studies systematically identifying mutants required for resistance to genotoxic agents (*2*, *3*). To further characterize Rtt109p, we generated a deletion mutant (table S1) and examined its sensitivities to a wider range of DNA-damaging agents. We found that *rtt109*Δ mutants were hypersensitive to agents that generate replication stress (Fig. 1A, top). We also observed hypersensitivity of *rtt109*Δ cells to continuous growth on plates containing phleomycin, an ionizing radiation (IR) mimetic that induces DNA double-strand breaks (DSBs). However, *rtt109*Δ cells were not markedly hypersensitive to acute IR treatment (Fig. 1A). Chronic DSB induction by phleomycin impinges on S-phase repair pathways, whereas most cells in an asynchronous culture, when subjected to acute IR treatment, arrest cell cycle progression and repair the DNA damage in G_2 (*4*). Together, these results suggest a role for Rtt109p in DNA damage tolerance during S phase.

In addition to displaying DNA-damage hypersensitivity, we observed that *rtt109*Δ cells were slow growing. Flow cytometric analysis of an asynchronous *rtt109*Δ culture revealed a high proportion of cells in the G_2-M stage of the cell cycle (Fig. 1B). Furthermore, the DNA content profile for *rtt109*Δ cells was much broader than for the wild type, revealing that cell growth continued despite slowed cell cycle progression. Cells lacking both *RTT109* and *MEC1* (which encodes the central DNA-damage checkpoint kinase) had a budding index equivalent to that of the wild-type strain (fig. S1), which indicates that the altered cell cycle profile of *rtt109*Δ cells reflects activation of the DNA-damage checkpoint. This was confirmed by the presence of partially phosphorylated DDR effector kinase Rad53p in *rtt109*Δ cells, indicative of chronic checkpoint activation (Fig. 1C).

Quantification of DSBs can be used to assess the presence of DNA damage in yeast cells (*5*, *6*). Strikingly, we found that Rad52-YFP foci—markers of DSBs—occur at much higher frequencies in *rtt109*Δ cells than in wild-type cells (Fig. 1D). Very few foci were seen in wild-type cells and unbudded *rtt109*Δ cells, whereas they occurred in around 40% and 75% of small-budded and large-budded *rtt109*Δ cells, corresponding to S and G_2 cells, respectively. These data therefore

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indicate increased spontaneously arising DNA damage in cells lacking Rtt109p, and suggest that such damage largely arises during S phase. To examine the effects of this DNA damage on genome stability, we measured rates of gross chromosomal rearrangements (GCRs) (*7*). Thus, we found that *RTT109* deletion increased GCR rates about ninefold compared with wild-type cells (Fig. 1E). As a further test for genome instability in *rtt109*Δ cells, we used a system to measure spontaneous recombination between tandem direct repeats (*8*). This revealed that *RTT109* deletion yields a moderate hyperrecombination phenotype, similar to that exhibited by an *sgs1*Δ hyperrecombination mutant (Fig. 1F). These data indicate that *rtt109*Δ mutants display increased genomic instability, possibly as a consequence of spontaneously arising DNA damage and, furthermore, suggest that this reflects defects in responding to and/or repairing DNA damage arising during S phase.

We noted that the phenotypes of *rtt109*Δ strains were similar to those reported for strains lacking the histone chaperone Asf1p (*9*, *10*) and that large-scale genetic network analyses had revealed that the genetic interaction profile of *RTT109* is highly similar to that of *ASF1* (*11*, *12*), which suggests they might act within the same pathway. Indeed, we found that the *rtt109*Δ *asf1*Δ double mutant was no more sensitive to hydroxyurea (HU) or methyl-methanesulfonate (MMS) than either single mutant (Fig. 2A). Although Asf1p stimulates histone deposition by the CAF-1 chromatin assembly complex in vitro (*13*), it also acts in a distinct and/or partially overlapping role in providing resistance to DNA-damaging agents (*14*). To address whether Rtt109p also acts synergistically with CAF-1, we combined the *RTT109* deletion with a disruption of *CAC1*, which encodes a CAF-1 subunit. As for *asf1*Δ *cac1*Δ cells, *rtt109*Δ *cac1*Δ cells were more sensitive to HU or MMS than the single-mutant strains. Furthermore, *rtt109*Δ *asf1*Δ *cac1*Δ cells were no more sensitive than *rtt109*Δ *cac1*Δ cells (Fig. 2A). From these data, we conclude that Rtt109p acts in the same pathway as Asf1p in providing resistance to DNA-damaging agents.

Given the reported role of Asf1p in promoting nucleosome assembly (*10*, *13*), we also analyzed the superhelical density of the 2μ plasmid in *rtt109*Δ cells. *RTT109* deletion caused a shift in the distribution of 2μ topoisomers, which indicated increased supercoiling compared with wild-type cells (Fig. 2B). Furthermore, a similar change in topoisomer distribution was caused by *ASF1* deletion, and no further change was seen in an *asf1*Δ *rtt109*Δ double-mutant strain. These results therefore indicate that Rtt109p and Asf1p act together in governing chromatin structure.

The DNA-damage hypersensitivity and slow growth of *asf1*Δ cells are associated with loss of acetylation on histone H3 lysine 56 (H3-K56) (*15*), but it has hitherto been unclear why K56 acetylation is absent in *asf1*Δ cells or which histone acetyltransferase (HAT) is responsible for acetylating this residue (*16*). Because of the epistatic relation between Asf1p and Rtt109p, we examined histone H3-K56 acetylation in *rtt109*Δ cells and found an absence of detectable K56 acetylation (Fig. 3A). Although either *RTT109* deletion or mutation of histone H3-K56 to arginine resulted in hypersensitivity toward HU, the double mutant was no more sensitive than the single mutants (Fig. 3B). Growth curves also revealed an epistatic relation between the two mutants (fig. S2), which indicates that the growth defect of *rtt109*Δ cells is due to loss of H3-K56 acetylation.

We reasoned that Rtt109p could either facilitate K56 acetylation or prevent K56 deacetylation by the known histone H3-K56 deacetylases Hst3p/Hst4p (*17*, *18*). We found that, despite elevated K56 acetylation in the absence of Hst3p and Hst4p, K56 acetylation was undetectable in a *hst3*Δ *hst4*Δ *rtt109*Δ triple-mutant strain (Fig. 3C), which suggested that Rtt109p acts

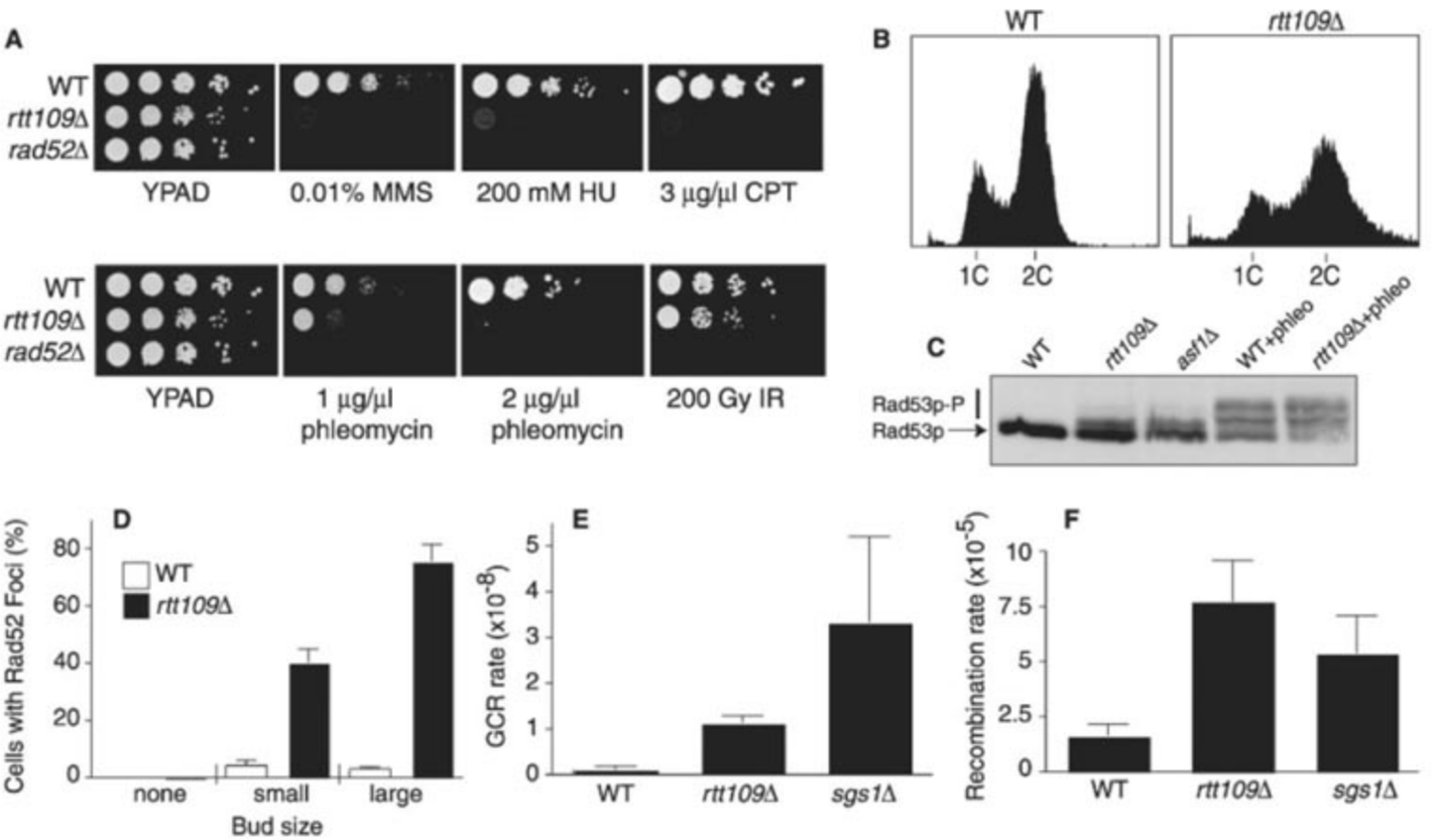
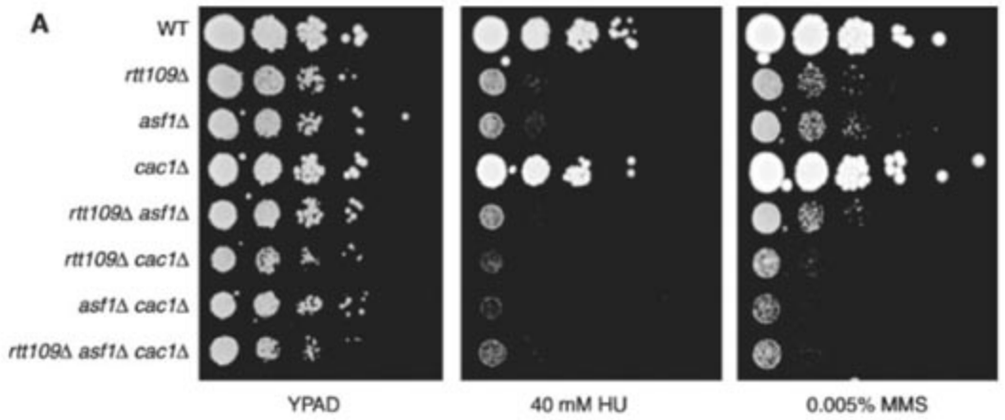


Fig. 1. *rtt109*Δ cells display hypersensitivity to DNA-damaging agents, DNA-damage checkpoint activation, and genomic instability. (**A**) Serial dilutions (10-fold) of the indicated mutants were spotted on yeast extract–peptone–dextrose medium with adenine (YPAD) alone or on YPAD containing the indicated drug (see text). (**B**) The DNA content of asynchronous cultures of wild-type (WT) and *rtt109*Δ strains was determined by flow cytometric analysis. (**C**) Electrophoretic mobility of Rad53p was analyzed in extracts from asynchronous cultures of wild-type (WT), *rtt109*Δ, and *asf1*Δ cells, and WT and *rtt109*Δ cells treated with phleomycin for 1 hour. (**D**) Cells displaying Rad52–yellow fluorescent protein (YFP) foci as a function of cell cycle position determined by bud size; the mean and standard deviation of two independent experiments are shown. (**E**) GCR frequency was measured for the indicated strains (*7*); the mean and standard deviation of three fluctuation tests are shown. (**F**) Recombination frequencies were measured in the indicated strains with a direct repeat recombination assay (*8*); the mean and standard deviation of three fluctuation tests are shown.



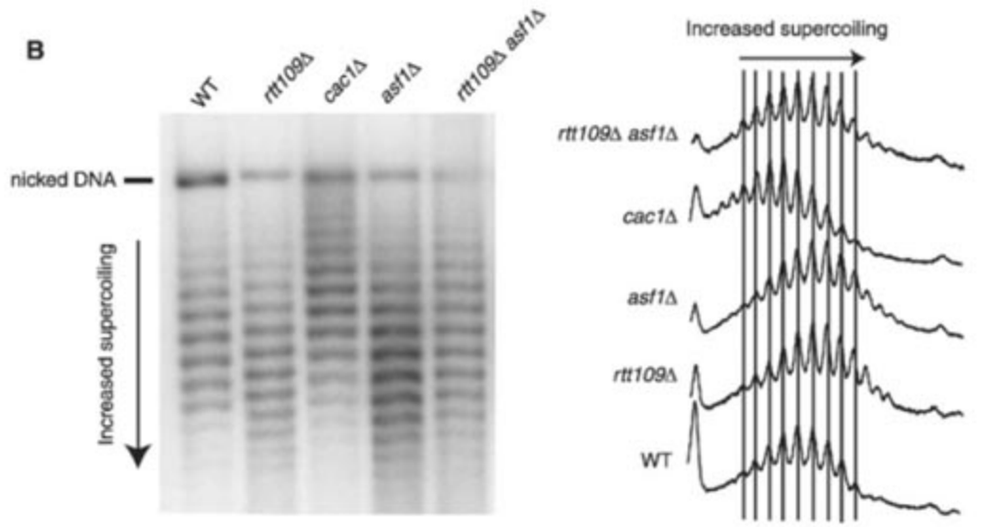
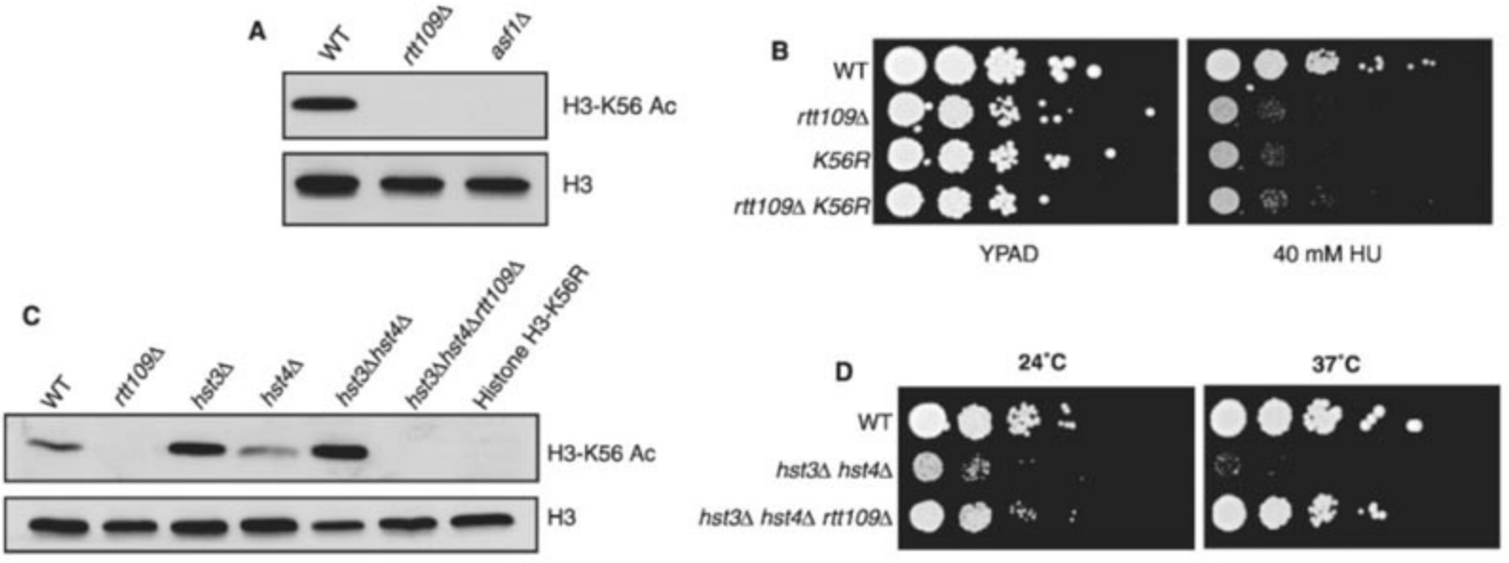


Fig. 2. Effects of *RTT109*, *ASF1*, and *CAC1* disruption on DNA damage sensitivity and 2μ plasmid supercoiling. (**A**) Serial dilutions (10-fold) of the indicated strains were plated on YPAD or YPAD containing HU or MMS. (**B**) DNA isolated from the indicated strains was electrophoresed on an agarose gel containing chloroquine. (Left) Superhelical density of the 2μ plasmid was analyzed by Southern blotting and hybridization with a radioactively labeled probe. (Right) Topoisomers were quantified by densitometric tracing.



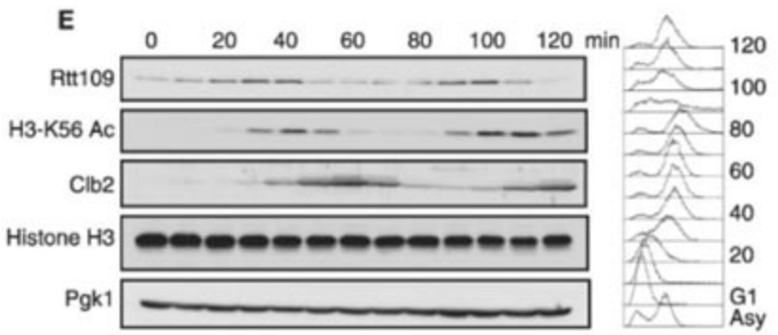


Fig. 3. Rtt109p is needed for histone H3-K56 acetylation in vivo. (**A**) Western blot analysis of whole-cell extracts isolated from the indicated strains was performed with antibodies specific for histone H3 or histone H3 acetylated on K56 (H3-K56 Ac). (**B**) Serial dilutions (10-fold) of the indicated strains were plated on YPAD or YPAD containing HU. (**C**) Whole-cell extracts from the indicated strains were probed with antibodies for histone H3 and histone H3-K56 Ac. (**D**) Serial dilutions (10-fold) of the indicated strains were plated on YPAD at the indicated temperature. (**E**) (Right) A strain expressing a hemagglutinin (HA)–tagged version of Rtt109p was arrested in G_1 with α-factor and released. Samples were taken at the indicated times for fluorescence-activated cell sorting (FACS). (Left) Western analysis was performed, probing for the indicated proteins with Pgk1p and histone H3 as loading controls and Clb2p as a G_2-M marker.

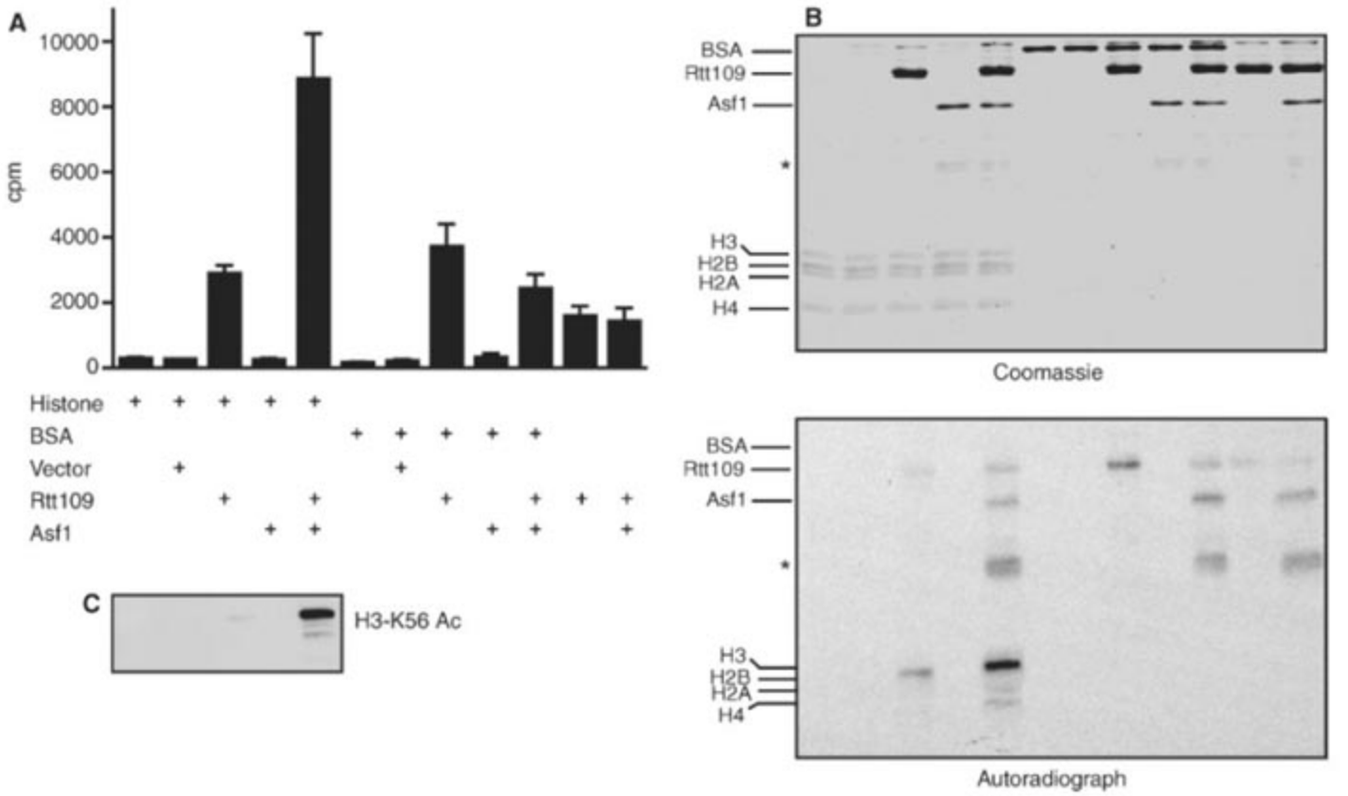


Fig. 4. Rtt109p displays histone acetyltransferase activity in vitro. (**A**) [^{3}H]Acetyl-CoA was incubated with histone octamers, bovine serum albumin (BSA), Rtt109p, or Asf1p as indicated. The ^{3}H counts were measured; the mean and standard deviation from six independent experiments are shown. (**B**) Half the reaction mixture from (A) was electrophoresed on an SDS-polyacrylamide gel, then stained with Coomassie brilliant blue (top), or was transferred onto a nitrocellulose membrane and subjected to autoradiography (bottom). Asterisks mark a degradation product of Asf1p. (**C**) Alternatively, a nitrocellulose membrane corresponding to the first five lanes of (B) was probed with an antibody against H3-K56 Ac.

to promote H3-K56 acetylation. Consistent with these findings and as reported for *ASF1* deletion (*17*), we observed that *RTT109* deletion suppressed the temperature-sensitive growth defect of a *hst3*Δ *hst4*Δ strain (Fig. 3D). Furthermore, because H3-K56 acetylation shows cell cycle control (*19*), we examined Rtt109p expression during cell cycle progression. Thus, we found that Rtt109p levels peak just before maximal K56 acetylation (Fig. 3E), as would be expected if Rtt109p is required for generating this modification.

To examine whether and how Rtt109p might mediate H3-K56 acetylation, we expressed and purified recombinant Rtt109p and Asf1p. Histone acetylation assays revealed that, although histone H3 acetylation took place with Rtt109p alone, this activity was enhanced in the presence of Asf1p (Fig. 4A). Autoradiographic analysis of the reactions also revealed that Rtt109p autoacetylates and weakly acetylates Asf1p, but not bovine serum albumin (Fig. 4B). Moreover, Western immunoblots of acetylation reactions probed with an antibody directed against acetylated H3-K56 revealed that Asf1p markedly stimulates the ability of Rtt109p to acetylate this site (Fig. 4C). This finding indicates that Asf1p governs the substrate specificity of Rtt109p. Because we have been unable to obtain evidence for a physical interaction between Asf1p and Rtt109p, we currently favor a model whereby an Asf1p-H3/H4 complex provides the optimal substrate for H3 acetylation by Rtt109p.

Taken together, our findings reveal that *S. cerevisiae* Rtt109p is the predominant HAT for histone H3-K56 in vivo and that this acetylation plays a critical role or roles in conferring resistance to spontaneously arising or experimentally induced DNA damage or replication stress. Notably, although the putative acetyl-CoA–binding sites of various previously known acetyltransferases display some sequence homologies with one another (*20*), we have not found significant homologies between these and Rtt109p. This raises the possibility that Rtt109p evolved catalytic activity independently of other known HATs and highlights the prospect of there being further as-yet-uncharacterized acetyltransferases that have not come to light through sequence analyses. Finally, our findings provide a mechanism for how Asf1 promotes histone H3 acetylation and thereby influences chromatin structure and genome stability.

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Supporting Online Material

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Rtt109 Acetylates Histone H3 Lysine 56 and Functions in DNA Replication

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Acetylation of histone H3 lysine 56 (H3-K56) occurs in S phase, and cells lacking H3-K56 acetylation are sensitive to DNA-damaging agents. However, the histone acetyltransferase (HAT) that catalyzes global H3-K56 acetylation has not been found. Here we show that regulation of Ty1 transposition gene product 109 (Rtt109) is an H3-K56 HAT. Cells lacking Rtt109 or expressing *rtt109* mutants with alterations at a conserved aspartate residue lose H3-K56 acetylation and exhibit increased sensitivity toward genotoxic agents, as well as elevated levels of spontaneous chromosome breaks. Thus, Rtt109, which shares no sequence homology with any other known HATs, is a unique HAT that acetylates H3-K56.

Nucleosomes are the basic repeat structure of eukaryotic chromatin, each consisting of ~146 base pairs of DNA wrapped around a histone octamer (*1*). Many diverse cellular functions are regulated through the modulation of nucleosome structure, and posttranslational modifications of core histones are key to this modulation (*2*–*4*). Indeed, histone modifications are known to play an important role in transcriptional regulation. However, the role of histone modifications in DNA replication is not well studied (*5*). Acetylation of lysine 56 on histone H3 (H3-K56) has been implicated in regulating replication, because H3-K56 is transiently acetylated during S phase. In addition, cells with alterations in H3-K56 acetylation display increased sensitivity toward certain DNA-damaging agents (*6*–*10*). Histone deacetylases responsible for deacetylating H3-K56 have recently been discovered (Hst3 and Hst4) (*11*, *12*), but the histone acetyltransferase (HAT) that globally acetylates H3-K56 has not been found (*8*).

To identify the H3-K56 HAT, we screened 4700 viable yeast deletion mutants for their effect on H3-K56 acetylation using antibodies that specifically recognize acetylated H3-K56 (*10*) (H3-K56Ac; Fig. 1A, top). From this screening procedure, two genes were identified that, when deleted, abolished H3-K56 acetylation: *ASF1* and *RTT109* (Fig. 1A). Western blot analysis of whole-cell extracts prepared from the *asf1*Δ and *rtt109*Δ mutant strains (table S1) confirmed that deletion of *ASF1* or *RTT109* abolishes H3-K56 acetylation. As a control, methylation of H3 lysine 79 was unaffected (Fig. 1B). Others have also recently shown that mutation of Asf1 abolishes acetylation of H3-K56 (*11*, *13*). However, Asf1 is a histone chaperone and does not appear to have intrinsic HAT activity (*14*).

RTT109 was originally identified in a genetic screen for regulators of transposition of the yeast retrotransposon Ty1 (*15*), but its biochemical function remained unknown. Therefore, we tested whether recombinant Rtt109 had HAT activity toward H3-K56. Purified recombinant Rtt109 was incubated with H3/H4 tetramers in the presence of [^{3}H]acetyl-coenzyme A (acetyl-CoA), and the incorporation of [^{3}H]acetate into proteins was analyzed. Indeed, Rtt109 incorporated [^{3}H]acetate into proteins (Fig. 2A) and did so in a concentration-dependent manner (fig. S1). Furthermore, Rtt109 acetylated itself and H3-K56, but not H4 (Fig. 2, B and C), in vitro. Similar to recombinant Rtt109, Rtt109 purified from yeast cells also acetylated H3-K56 (Fig. 2D and fig. S2). Thus, Rtt109, both in recombinant form and as a complex purified from yeast cells, exhibits HAT activity toward H3-K56, but not H4, in vitro.

Analysis of the amino acid sequence of Rtt109 did not reveal homology to the catalytic domain of any known HATs. Canonical HATs such as Gcn5 and Esa1 use a glutamate residue conserved in each HAT family to deprotonate lysines before acetylation (*16*). We reasoned that Rtt109 may use a negatively charged residue for catalysis in a similar manner. Thus, we made 11 site-specific *rtt109* mutants by replacing aspartate (D) and glutamate (E) residues with alanines (A) (fig. S3) and tested their effects on H3-K56 acetylation in yeast cells. Nine of these mutants had little effect on H3-K56 acetylation (fig. S4), but two, *D89A* and *DD287 288AA*, resulted in the loss of H3-K56 acetylation in yeast cells (Fig. 2E). Each of these three aspartate residues was then mutated to asparagine (N). The *D89N* mutant cells lost H3-K56 acetylation, and the *DD287 288NN* mutant cells exhibited a significant reduction in H3-K56 acetylation, whereas the *D287N* and *D288N* mutants had little effect (Fig. 2E). Consistent with the effect of these mutants on H3-K56 acetylation in yeast cells, in vitro HAT assays revealed that the Rtt109 mutant proteins D89A, D89N, and DD287 288AA lost the ability to acetylate H3, whereas the Rtt109 mutant DD287 288NN exhibited a reduced level of HAT activity, and the single mutants D287N and D288N had similar levels of activity compared with wild-type enzyme (Fig. 2, F and G). The inability of Rtt109 mutants to acetylate H3 was not likely due to disruption of the overall structure of the mutant proteins, because these Rtt109 mutants still bound Vps75, a known Rtt109-interacting protein (*17*) (Fig. 2H). These results demonstrate that D89 is essential for the HAT activity, whereas D287 and D288 are not essential, but contribute to this activity. D89 may serve as the deprotonation residue, and D287 and D288 may serve other functions such as binding to histones and/or acetyl-CoA. All of these aspartate residues are conserved among the Rtt109 family members (fig. S3).

Yeast cells expressing mutants lacking H3-K56 acetylation (K56A, K56R) display increased sensitivity toward DNA-damaging agents (*6*, *8*), including camptothecin (CPT), hydroxyurea (HU), and methyl-methanesulfonate (MMS) (*16*). There-

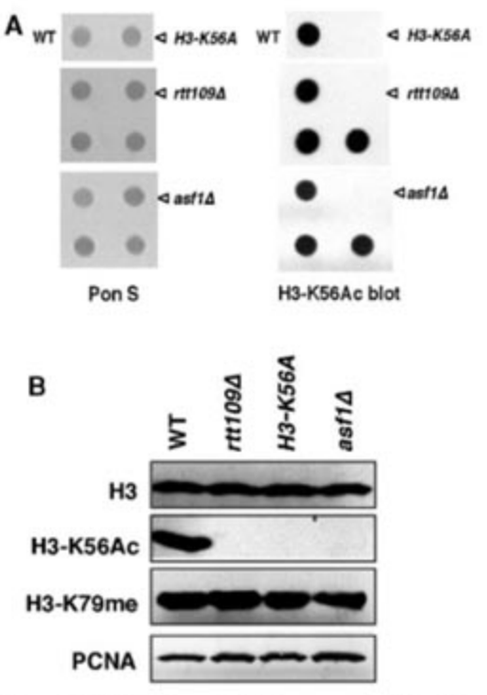

Fig. 1. (**A**) Rtt109 and Asf1 are required for H3-K56 acetylation. The total amount of protein from yeast cell extracts was revealed by Ponceau S staining (Pon S, left panel) and H3-K56 acetylation was detected by Western blot with antibodies that recognize H3 acetylated at lysine 56 (H3-K56Ac, right panel). Membrane regions surrounding the spots corresponding to *H3-K56A*, *rtt109*Δ, *asf1*Δ (arrowheads), and wild-type (WT) cells are shown. (**B**) Acetylation of H3-K56 is not detected in *H3-K56A*, *rtt109*Δ, and *asf1*Δ mutant cells. Western blot was performed to examine whole-cell extracts from cells as shown, with antibodies against histone H3 (H3), H3-K56Ac, H3 methylated at lysine 79 (H3-K79me), and PCNA.

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fore, the sensitivity of *rtt109Δ* cells and *rtt109* site-specific mutant cells to these genotoxic agents was determined. The *rtt109Δ* cells and cells expressing *rtt109* aspartate mutants (*D89A*, *D89N*, and *DD287 288AA*) that lacked H3-K56 acetylation exhibited sensitivity toward CPT, HU, and MMS to a degree similar to cells expressing the *H3-K56* mutants. Furthermore, the *DD287 288NN* cells, where H3-K56 acetylation was

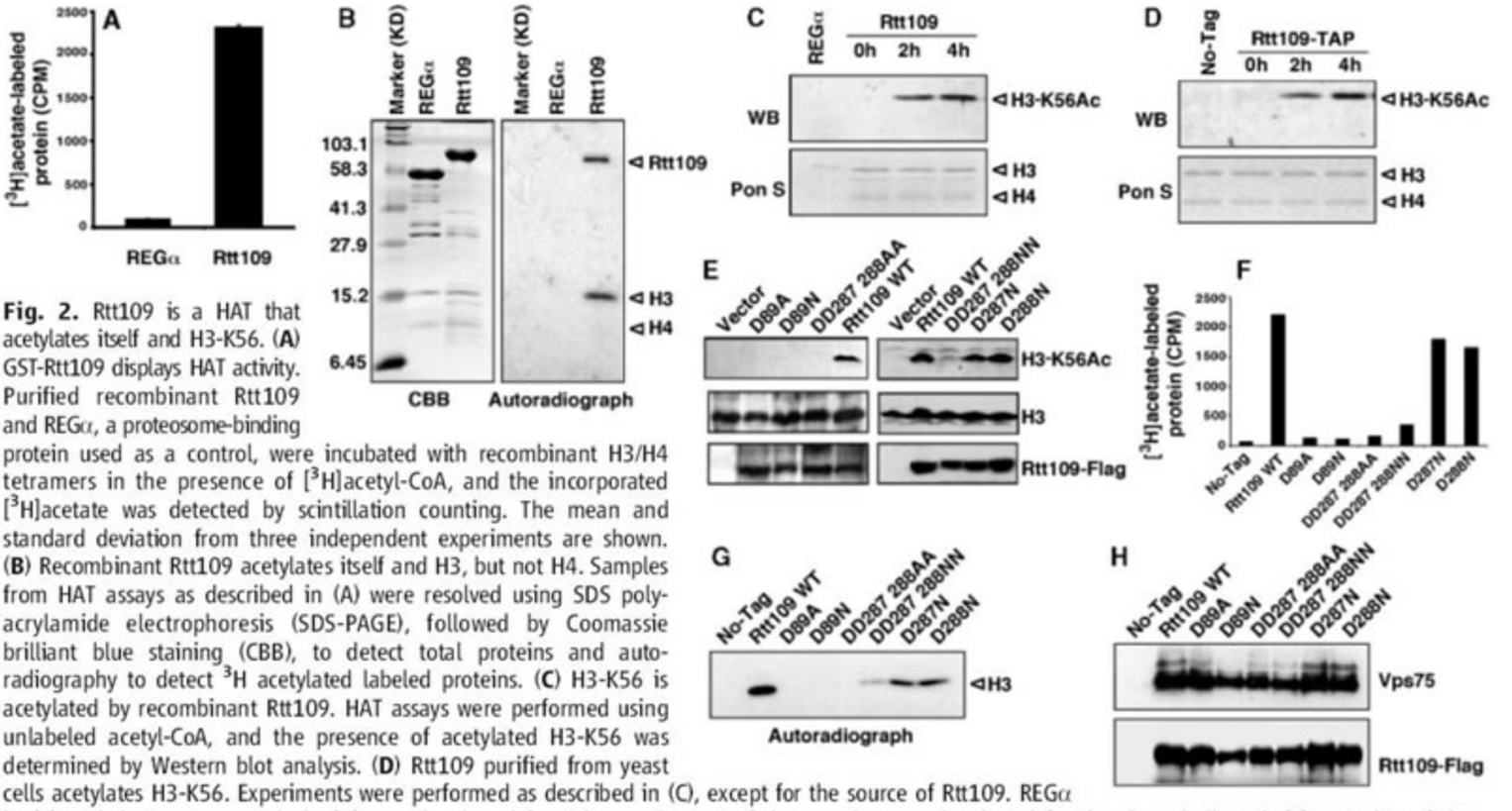

Fig. 2. Rtt109 is a HAT that acetylates itself and H3-K56. (**A**) GST-Rtt109 displays HAT activity. Purified recombinant Rtt109 and REGα, a proteosome-binding protein used as a control, were incubated with recombinant H3/H4 tetramers in the presence of [^{3}H]acetyl-CoA, and the incorporated [^{3}H]acetate was detected by scintillation counting. The mean and standard deviation from three independent experiments are shown. (**B**) Recombinant Rtt109 acetylates itself and H3, but not H4. Samples from HAT assays as described in (A) were resolved using SDS polyacrylamide electrophoresis (SDS-PAGE), followed by Coomassie brilliant blue staining (CBB), to detect total proteins and autoradiography to detect ^{3}H acetylated labeled proteins. (**C**) H3-K56 is acetylated by recombinant Rtt109. HAT assays were performed using unlabeled acetyl-CoA, and the presence of acetylated H3-K56 was determined by Western blot analysis. (**D**) Rtt109 purified from yeast cells acetylates H3-K56. Experiments were performed as described in (C), except for the source of Rtt109. REGα in (C) and the No-tag sample in (D) were incubated for 6 hours; the rest of the samples were incubated for the times indicated. (**E**) Mutation of three conserved aspartate residues affects H3-K56 acetylation. Acetylation of H3-K56 was analyzed in yeast cells expressing *rtt109* mutants of the indicated conserved aspartate residues. (**F** and **G**) In vitro assays using Rtt109 mutant proteins purified from yeast cells show a loss of HAT activity by selected aspartate mutants. (**H**) Rtt109 mutant proteins interact with Vps75. Vps75-TAP (tandem affinity purification) was purified from wild-type or *rtt109* mutant cells, and copurified Rtt109 or mutants were detected by Western blot.

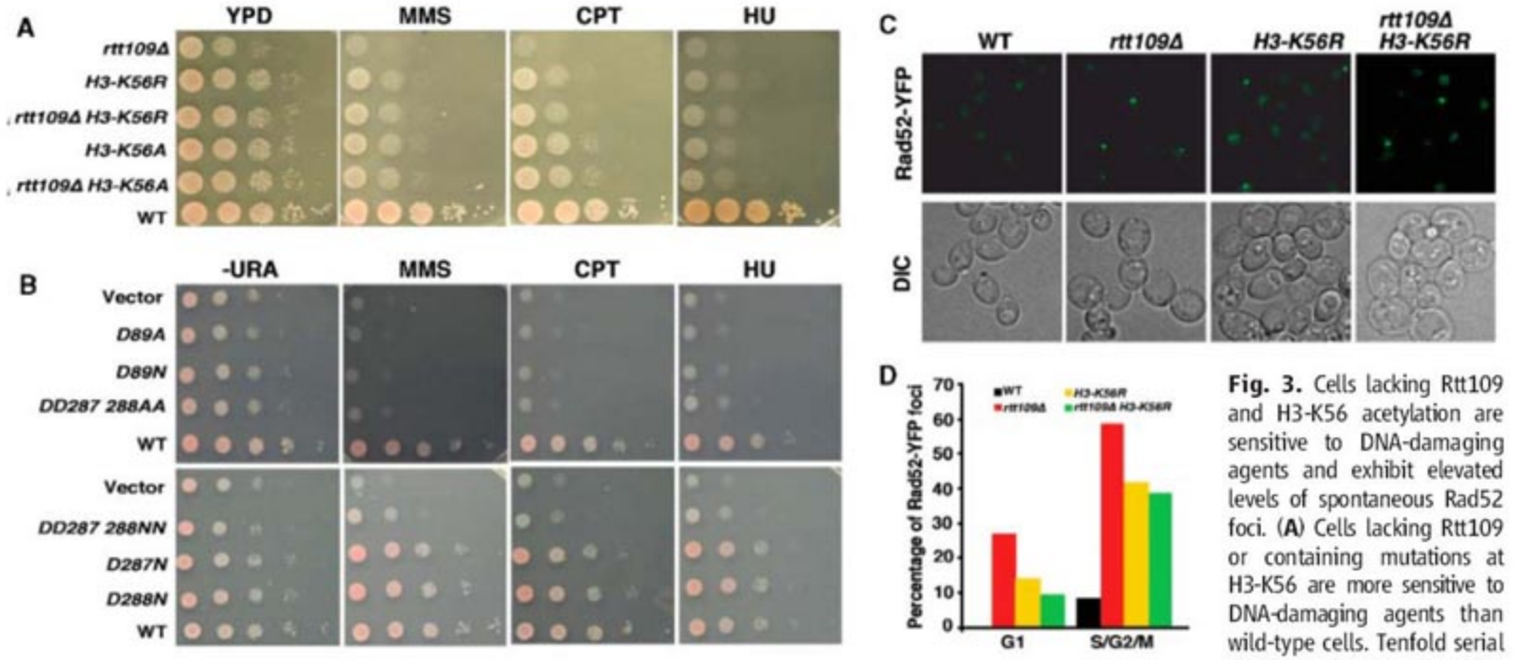

Fig. 3. Cells lacking Rtt109 and H3-K56 acetylation are sensitive to DNA-damaging agents and exhibit elevated levels of spontaneous Rad52 foci. (**A**) Cells lacking Rtt109 or containing mutations at H3-K56 are more sensitive to DNA-damaging agents than wild-type cells. Tenfold serial dilutions of yeast cells of the genotype indicated at the left were spotted onto YPD medium alone or YPD medium containing CPT, HU, or MMS. Note that the *rtt109Δ H3-K56R* mutant cells grew slightly better than *rtt109Δ* single mutant cells when H3 and H4 were expressed on a plasmid. (**B**) Cells expressing *rtt109* mutants unable to acetylate H3-K56 display a similar sensitivity toward DNA-damaging agents as the *rtt109Δ* mutant cells. (**C** and **D**) Asynchronous *rtt109Δ* and *H3-K56R* mutant cells exhibit an increase in the percentage of cells containing Rad52-YFP foci compared with WT cells. Rad52-YFP and differential interference contrast images from a representative field of WT and various mutants are shown (C), and the percentage of cells containing Rad52 foci are calculated (D). Cells were separated into two categories on the basis of whether a cell displayed a bud (S/G_2/M) or not (G_1).

reduced but not abolished, were not as sensitive as *rtt109*Δ cells (Fig. 3, A and B). Moreover, *rtt109*Δ *H3-K56R* and *rtt109*Δ *H3-K56A* double-mutant cells displayed similar sensitivities toward these DNA-damaging agents as either single mutant alone (Fig. 3A and fig. S5). In contrast, cells expressing *rtt109* site-specific mutants where H3-K56 acetylation was not affected were resistant to these DNA-damaging agents (Fig. 3B and fig. S6). These results suggest that the ability of Rtt109 to suppress sensitivity toward DNA-damaging agents is mainly mediated by its HAT activity toward H3-K56.

In budding yeast, Rad52 forms spontaneous foci, predominantly during S and G_2-M phases of the cell cycle, and these foci are thought to be sites of repair of DNA lesions (*18*, *19*). Cells with mutations in proteins involved in DNA metabolism, such as Top3 exhibit elevated levels of Rad52 foci, possibly due to an increase in spontaneous chromosome breaks (*20*). The *rtt109*Δ and *H3-K56R* single- and double-mutant cells showed a substantial increase in Rad52 fused with yellow fluorescent protein (Rad52-YFP) foci (Fig. 3, C and D). Moreover, the *rtt109*Δ H3-K56R double-mutant cells did not exhibit more Rad52 foci than either *rtt109*Δ or *H3-K56R* mutant alone (Fig. 3D). Thus, the increase in Rad52-YFP foci observed in *rtt109*Δ mutant cells appears mainly to be due to loss of H3-K56 acetylation. Supporting this idea, acetylation of four other H3 lysine residues (K9, K14, K18, and K23) was not altered in the *rtt109*Δ mutant cells (fig. S7). Taken together, these data indicate that Rtt109-mediated acetylation of H3-K56 during S phase protects DNA from damage.

Here we have shown that Rtt109 is a member of a novel HAT family that acetylates H3-K56. The *rtt109*Δ mutant exhibited a synthetic lethal or slow-growth phenotype with a mutant allele of PCNA (proliferating cell nuclear antigen), *pol30-79*, which is defective in DNA replication and repair (*21*), but not with the PCNA mutant allele, *pol30-8*, which is defective in epigenetic silencing (*22*) (fig. S8A). The *rtt109*Δ mutant also exhibited a synthetic lethal/slow growth phenotype with a mutation in DNA polymerase α (fig. S8B) and was previously found to genetically interact with Orc2 and Cdc45 mutations (*23*, *24*). All of these proteins are involved in DNA replication. The genetic interactions between Rtt109 and the proteins involved in DNA replication suggest that the *rtt109*Δ mutant cells are defective in certain aspects of DNA replication. In support of this idea, the *rtt109*Δ mutant exhibits synthetic lethal or slow-growth phenotypes with mutations in genes such as *RAD52*, which are involved in homologous recombination (*25*), a process that is needed to resolve stalled replication forks (*26*). Thus, H3-K56 acetylation by Rtt109 is closely linked to DNA replication.

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A Two–Amino Acid Change in the Hemagglutinin of the 1918 Influenza Virus Abolishes Transmission

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The 1918 influenza pandemic was a catastrophic series of virus outbreaks that spread across the globe. Here, we show that only a modest change in the 1918 influenza hemagglutinin receptor binding site alters the transmissibility of this pandemic virus. Two amino acid mutations that cause a switch in receptor binding preference from the human α-2,6 to the avian α-2,3 sialic acid resulted in a virus incapable of respiratory droplet transmission between ferrets but that maintained its lethality and replication efficiency in the upper respiratory tract. Furthermore, poor transmission of a 1918 virus with dual α-2,6 and α-2,3 specificity suggests that a predominant human α-2,6 sialic acid binding preference is essential for optimal transmission of this pandemic virus. These findings confirm an essential role of hemagglutinin receptor specificity for the transmission of influenza viruses among mammals.

The "Spanish" influenza pandemic virus spread globally and resulted in the deaths of up to 50 million people worldwide (*1*, *2*). The ability of this H1N1 pandemic strain to spread rapidly and cause high rates of illness among humans makes it valuable for studying the molecular properties that confer efficient transmissibility of influenza viruses. An influenza virus bearing all eight gene segments of the 1918 pandemic virus was recently generated in cultured cells, was found to be lethal for chicken embryos and mice, and displayed a high-growth phenotype in human lung cells. Furthermore, the 1918 hemagglutinin (HA) and polymerase genes were shown to be essential for maximal virus replication and optimal virulence (*3*–*5*).

Influenza pandemics seem to occur every 10 to 40 years, but the factors that lead to the emergence of pandemic viruses are complex and poorly understood. However, the establishment of efficient and sustained human-to-human transmission of a virus to which humans have

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little or no preexisting immunity is a fundamental property of pandemic strains (*6*, *7*). Most threatening is the possibility of another pandemic, similar to that experienced in 1918, caused by a novel influenza subtype virus capable of causing severe respiratory disease and death. The avian influenza H5N1 virus, which has resulted in more than 250 human infections (*8*), has not acquired human influenza virus genes and lacks the ability to spread efficiently from human to human (*9*, *10*). Reassortment of avian H5N1 virus genes with human H3N2 influenza virus genes was shown to be insufficient for transmission of this avian virus (*11*), suggesting that additional unknown mutations are required for H5N1 to emerge as a pandemic strain.

The binding of influenza viruses to their target cells is mediated by the viral HA, which recognizes cell surface glycoconjugates containing terminal sialic acid (SA) residues. Avian influenza viruses preferentially bind SA linked to galactose by an α-2,3 linkage (α2,3 SA), which is found in high concentrations on the epithelial cells of the intestine of waterfowl and shorebirds (*12*). Conversely, human influenza viruses (H1 to H3 subtypes) more readily bind to receptors that contain terminal α-2,6-linked sialyl-galactosyl (α2,6 SA) moieties that are found on the human respiratory tract epithelium (*13*, *14*). The three influenza pandemic viruses of the last century, occurring in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2), each possessed an HA with a human α2,6 SA binding preference and are thought to have originated from an avian virus possessing the α2,3 SA binding preference (*13*–*16*). It has been postulated that the lack of sustained human-to-human transmission of avian influenza H5N1 viruses is due to their α2,3 SA receptor binding preference (*17*–*19*). Higher proportions of α2,3 SA receptors in the human lower respiratory tract compared with the upper respiratory tract may explain the severity of H5N1 viral pneumonia in humans resulting from H5N1 viral attachment deep in the lungs (*17*, *19*).

Amino acids at positions 190 and 225 in the 1918 pandemic influenza virus HA determine its receptor binding specificity (*15*, *16*). In this study, we generated recombinant influenza viruses possessing all eight gene segments of the 1918 influenza virus to examine the role of receptor binding specificity on replication, pathogenicity, and transmissibility of this pandemic strain. We generated two variant A/South Carolina/1/18 (SC18) 1918 viruses in which the HA was altered to change the receptor binding specificity from the parental human α2,6 SA (SC18) receptor preference to an avian α2,3 SA receptor preference (AV18) or a mixed α2,6 and α2,3 SA specificity reflecting the A/New York/1/18 (NY18) virus binding specificity. The NY18 virus was a natural variant sequenced from an archived lung tissue sample prepared during autopsy of a patient who died within 6 days of hospitalization in September 1918 (*20*). The HA corresponding to NY18 virus was made by introducing a single amino acid substitution [Asp^{225}→Gly^{225} (D225G)] in the SC18 HA. The AV18 virus, which differs by one amino acid from NY18 virus, was made by introducing an additional amino acid change [Asp^{190}→Glu^{190} (D190E)] within the NY18 HA. Compared with the SC18 virus, the AV18 variant has two amino acid changes (D190E and D225G) in the HA, which matches the conserved avian consensus sequence in the receptor binding site and which converts it to the classic α2,3 SA receptor preference (*15*). A/Duck/Alberta/35/76 (Dk/Alb) and A/Texas/36/91 (Tx/91) viruses were included in the study as controls representative of an avian

Table 1. Titer of virus stocks prepared on MDCK cells with trypsin (1 μg/ml, Sigma) and incubated at 37°C with 5% CO_2 for 48 hours. Hemagglutination assay of viruses used 0.5% α-2,3-resialylated CRBCs, α-2,6-resialylated CRBCs, or untreated CRBCs. The results shown correspond to four hemagglutination units. Similar results were obtained when viruses were adjusted to 8, 16, or 32 hemagglutination units with untreated CRBCs.

	Amino acid position (H3 numbering)			Presence or absence of hemagglutination		
	190	225	Infectivity titer (pfu/ml)	α2,6 CRBCs	α2,3 CRBCs	Untreated CRBCs
SC18	D	D	4.8×10^7	+	−	+
NY18	D	G	3.3×10^7	+	+	+
AV18	E	G	5.0×10^7	−	+	+
Dk/Alb	E	G	2.2×10^7	−	+	+

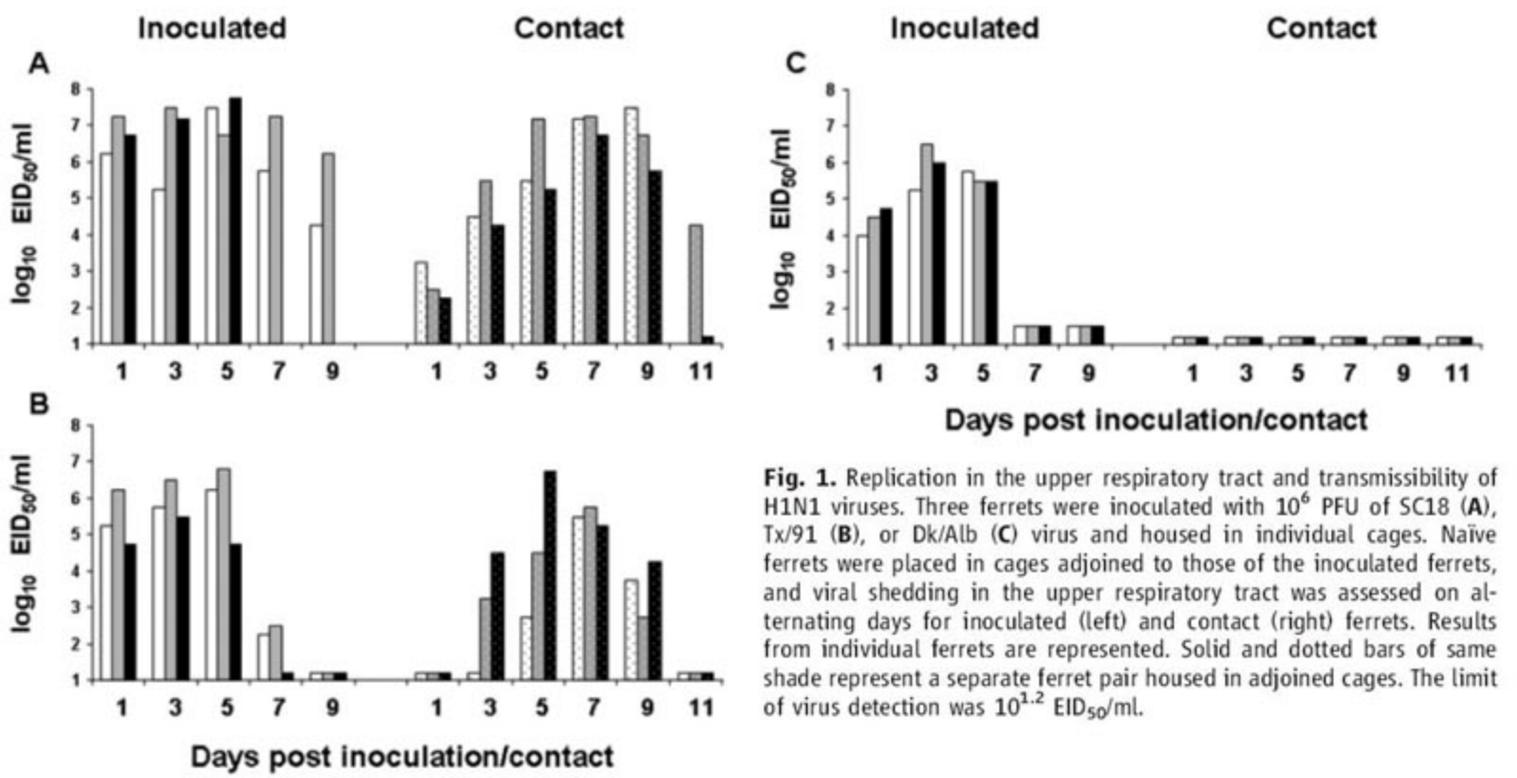

Fig. 1. Replication in the upper respiratory tract and transmissibility of H1N1 viruses. Three ferrets were inoculated with 10^6 PFU of SC18 (**A**), Tx/91 (**B**), or Dk/Alb (**C**) virus and housed in individual cages. Naïve ferrets were placed in cages adjoined to those of the inoculated ferrets, and viral shedding in the upper respiratory tract was assessed on alternating days for inoculated (left) and contact (right) ferrets. Results from individual ferrets are represented. Solid and dotted bars of same shade represent a separate ferret pair housed in adjoined cages. The limit of virus detection was $10^{1.2}$ EID_{50}/ml.

H1N1 virus and a human H1N1 virus, respectively. The 1918 viruses were generated by using the previously described reverse genetics system (*21*–*23*), and the identities of virus genes in the rescued viruses were confirmed by reverse transcription polymerase chain reaction and sequence analysis.

The rescued 1918 viruses containing the parental SC18 HA and the two variant HAs had similarly high infectivity titers in Madin-Darby canine kidney (MDCK) cells (Table 1). The receptor-binding properties of the 1918 viruses were confirmed in HA assays by using enzymatically modified chicken red blood cells (CRBCs) that contain either α2,3 or α2,6 SA, as previously described (*15*). The AV18 virus and the avian Dk/Alb control virus hemagglutinated the α2,3-resialylated CRBCs only, whereas the SC18 virus hemagglutinated the α2,6-resialylated CRBCs only. The NY18 virus hemagglutinated both α2,3- and α2,6-resialylated CRBCs.

Pathogenesis and transmissibility of the parental 1918 (SC18) virus were evaluated and compared with those of Tx/91 virus with an α2,6 SA receptor binding preference (*16*) and with those of the avian Dk/Alb virus possessing an α2,3 SA receptor binding preference (Table 1) (*24*). Ferrets were housed in adjacent cages that prevented direct and indirect contact between animals but allowed spread of influenza virus through the air (*11*, *25*). They were inoculated intranasally with 10^6 PFU (plaque forming units). One day after infection, three naïve ferrets housed in transmission cages were placed adjacent to each of the three inoculated ferrets (*26*). Three additional inoculated ferrets from each virus-infected group were killed on day 3 postinoculation (p.i.) for assessment of pathologic and virologic parameters (*26*). Ferrets inoculated with the parental SC18 virus shed high titers of infectious virus in nasal washes beginning as early as day 1 p.i. [50% egg infectious dose (EID_{50}/ml) from $10^{6.25}$ to $10^{7.25}$], and they sustained titers of $\geq 10^{4.5}$ EID_{50}/ml for 9 days p.i. (Fig. 1A, left). SC18 virus caused severe disease in all inoculated ferrets starting 2 days p.i.; symptoms included lethargy, anorexia, rhinorrhea, sneezing, severe weight loss (Table 2 and fig S1), and high fever, and two of the three animals died by day 11 p.i. Ferrets inoculated with H1N1 Tx/91 and Dk/Alb also shed high titers of virus in nasal washes (peak titers had EID_{50}/ml values from $10^{5.5}$ to $10^{6.8}$), but they were able to clear the virus from the upper respiratory tract by day 9 p.i. (Fig. 1, B and C) after displaying minimal symptoms (Table 2).

The human SC18 and Tx/91 viruses efficiently transmitted to each of the three contact ferrets (Fig. 1, A and B, right). The SC18 virus was detected in the contact ferrets as early as day 1 postcontact (p.c.), whereas the Tx/91 virus required 3 to 5 days to achieve detectable virus titers in nasal washes of the Tx/91 contact ferrets. The Tx/91 contact ferrets exhibited little morbidity, whereas all three SC18 contact ferrets exhibited severe signs of illness and weight loss, and one of three contact animals failed to clear the virus before it succumbed to infection on day 6 p.c. In contrast to the efficient spread of SC18 and Tx/91 viruses, the avian Dk/Alb virus was not transmitted to naïve contact ferrets, because virus was not detected in the nasal washes from the contact ferrets at any time. Furthermore, seroconversion was not detected by hemagglutination inhibition (HI) analysis of postexposure sera (Table 2). Both A/Duck/New York/15024/96 and A/Turkey/South Dakota/7034/86, which are representative avian viruses with an α2,3 SA receptor preference, exhibited efficient replication in the upper respiratory tract, but no transmission was detected between ferrets.

We introduced one– and two–amino acid substitutions into the 1918 virus HA to produce SC18 variants NY18 and AV18, respectively. A switch in receptor specificity from an α2,6 SA

Table 2. Clinical symptoms, virus replication, seroconversion, and transmissibility among ferrets inoculated with H1N1 viruses and among ferrets exposed to the inoculated animals (contacts). The percentage of mean maximum weight loss is shown. NW, nasal wash.

	Inoculated ferrets Number with characteristic/total number				Contact ferrets Number with characteristic/total number			Respiratory droplet transmission
	Sneezing (day of onset)	Weight loss (%)	Virus detected in NW	Seroconversion (range of HI antibody titer)	Weight loss (%)	Virus detected in NW	Seroconversion (range of HI antibody titer)	
SC18	3/3 (2)	3/3 (11.7)	3/3	1/1 (1280)*	2/3 (15.4)	3/3	3/3 (80–640)	Efficient
Tx/91	3/3 (2)	3/3 (6.2)	3/3	3/3 (160–640)	3/3 (3.5)	3/3	3/3 (160–320)	Efficient
Dk/Alb	2/3 (5)	2/3 (1.2)	3/3	3/3 (80–1280)	0/3	0/3	0/3	None
AV18	0/3	3/3 (14.7)	3/3	1/1 (640)*	0/3	0/3	0/3	None
NY18	0/3	3/3 (18.9)	3/3	2/2 (320–640)†	1/3 (1.4)	1/3	2/3 (40–80)	Inefficient

*Only one ferret survived and was tested. †Two ferrets survived and were tested.

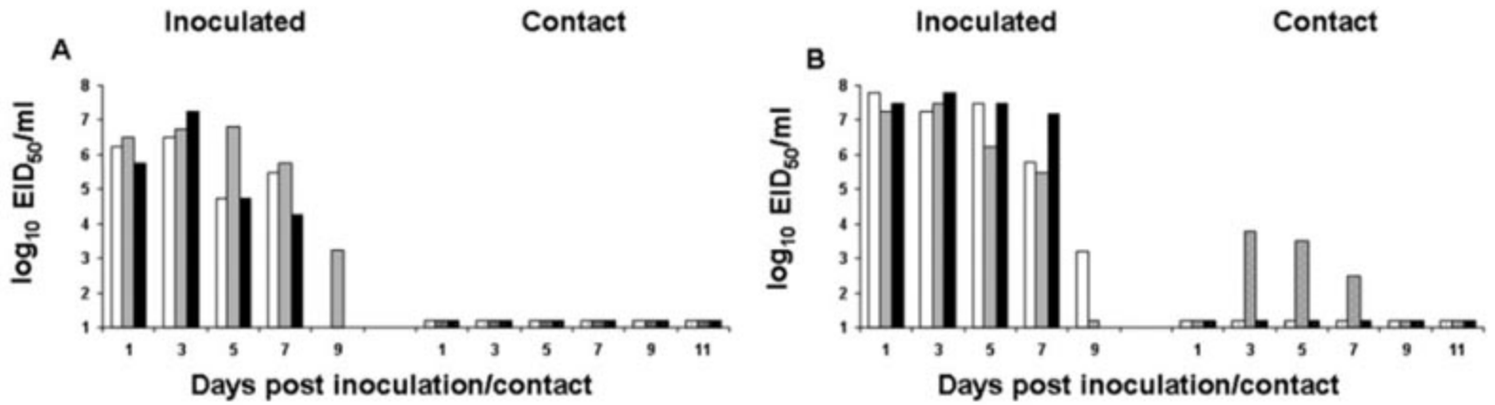

Fig. 2. Respiratory droplet transmissibility of 1918 viruses with mutated HA proteins. Three ferrets were inoculated with 10^6 PFU of AV18 (**A**) or NY18 (**B**) virus and placed in separate cages. Naïve ferrets were placed in cages adjoined to those of the inoculated ferrets, and viral shedding in the upper respiratory tract was assessed on alternating days for inoculated (left) and contact (right) ferrets. Results from individual ferrets are represented. Solid and dotted bars of same shade represent a separate ferret pair housed in adjoined cages.

(human) to an α2,3 SA (avian) binding preference abolished the transmissibility of the pandemic virus (Fig. 2 and Table 2). Although ferrets inoculated with AV18 virus exhibited severe illness (Table 2 and fig S1) and shed high titers of infectious virus in nasal washes (Fig. 2A, left), none of the three AV18 contact ferrets had detectable virus in nasal washes, and post-exposure sera collected from contact animals lacked antibodies against AV18. The NY18 virus, with dual α2,6 and α2,3 SA specificity, also resulted in severe illness and death among the inoculated ferrets, but it failed to transmit efficiently, as evidenced by the paucity of clinical symptoms and virus shedding among the contact ferrets (Fig. 2B). Two of the three NY18 contact ferrets seroconverted with relatively low HI titers of 40 and 80 (Table 2). The lack of efficient transmission was not due to the inability of the NY18 virus to replicate to high titers in the upper respiratory tract, including the nasal turbinates (Fig. 2B, left, and fig S2). Interestingly, no sneezing was noted among the AV18- and NY18-inoculated ferrets through a 14-day observation period, a finding consistent with the lack of notable sneezing observed in ferrets infected with H5N1 viruses (*11*).

Despite the differences in transmissibility of the parental 1918 (SC18) virus and the mutant 1918 viruses, similar damage to multiple lung lobes was observed 3 days after intranasal infection (*26*) (Fig. 3). Ferret lungs infected with SC18, AV18, and NY18 viruses exhibited necrotizing bronchiolitis and moderate to severe alveolitis with edema (Fig. 3, A to E, I, and J). Viral antigen was common in lung tissues, with localization in the upper to lower portions of the bronchial airways, bronchial and bronchiolar epithelium, and hyperplasic epithelium within alveoli (Fig. 3, F to H). Ferrets inoculated with control Tx/91 and Dk/Alb viruses generally showed a lack of significant lung lesions (Fig. 3, K to M).

Receptor binding, the initial event in influenza virus infection, was a major determinant of virus transmission efficiency of the H1N1 pandemic virus. This work also evaluates the virulence of the 1918 virus in a ferret model, a model that is believed to be more representative than the mouse model of disease caused by influenza viruses in humans. In contrast to other human influenza virus strains, the 1918 virus demonstrated uniquely high virulence and lethality in ferrets. The mutant 1918 virus possessing α2,3 SA receptor binding (AV18) was equally virulent in ferrets as the parental SC18 strain at the dose administered. Remarkably, the AV18 virus replicated in the upper respiratory tract as efficiently as the parental SC18 virus, but it failed to transmit to contact ferrets. Moreover, a human α2,6 SA binding preference is essential for optimal transmission of this exceptionally virulent virus. The introduction of a single mutation that converts the HA to dual α2,6 and α2,3 SA binding specificity (NY18) reduced the high transmissibility observed with the parental 1918 (SC18) virus. This result is consistent with the previously demonstrated lack of transmissibility of an H5N1 2003 virus that possessed dual α2,6 and α2,3 SA specificity due to a naturally acquired mutation at HA residue 223 (H5 numbering; residue 227 by H3 numbering) (*11*, *27*).

Our findings raise the possibility that, to become more transmissible, the currently circulating avian influenza H5N1 virus may require a receptor binding change to a predominant α2,6 SA binding preference. Such a modification of H5 HA may result in improved virus binding to

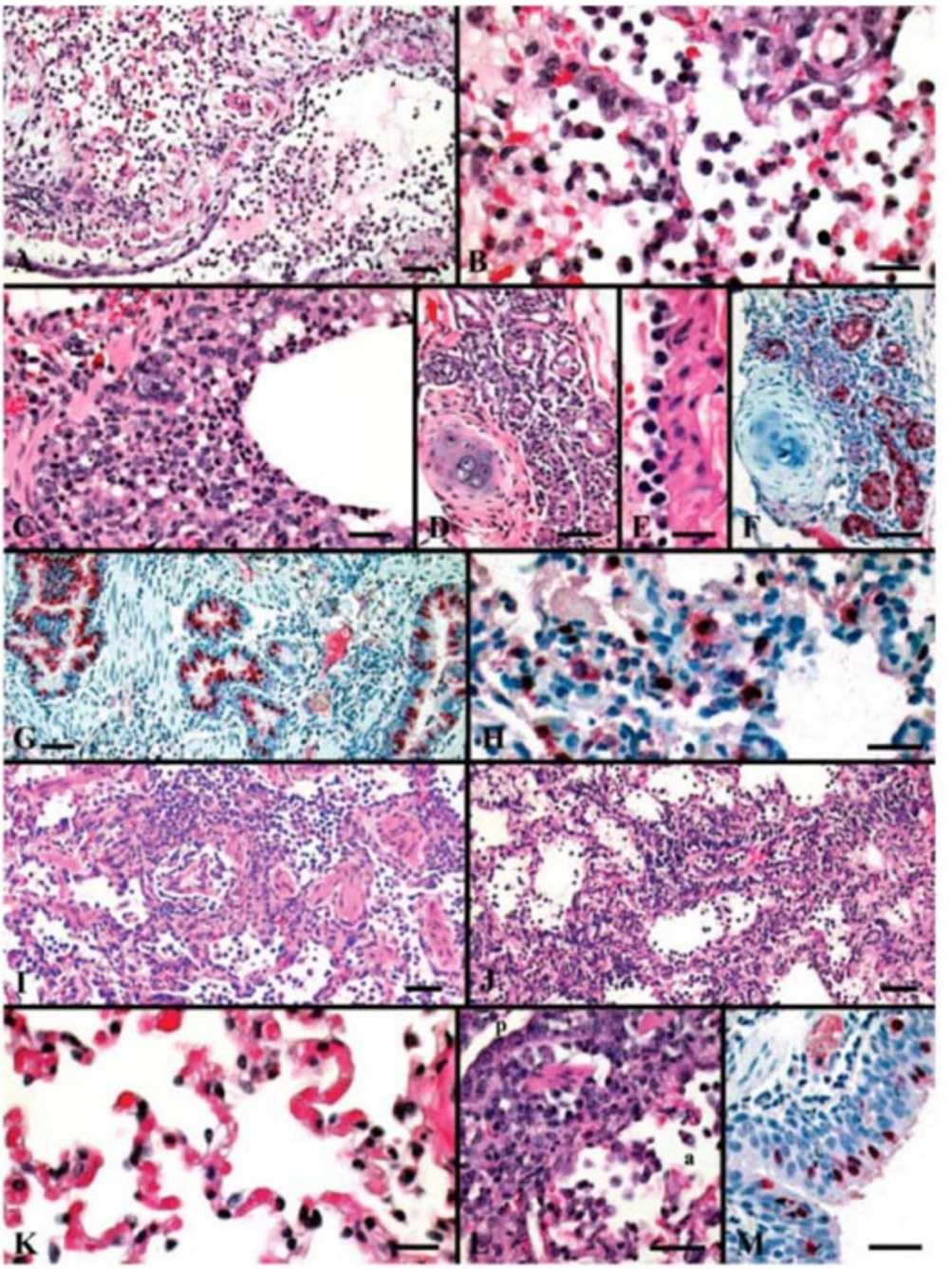

Fig. 3. Photomicrographs of hematoxylin and eosin [(A) to (E) and (I) to (L)] and immunohistochemically [(F) to (H) and (M)] stained lung sections from influenza virus–infected ferrets sampled on day 3 after inoculation. (**A** to **H**) Lung sections infected by SC18 virus. (A) Severe necrotizing bronchiolitis with severe diffuse alveolitis and edema. Scale bar indicates 50 μm. (B) Severe diffuse alveolitis; scale bar, 20 μm. (C) Necrotizing bronchiolitis; scale bar, 30 μm. (D) Necrosis and (F) associated influenza viral antigen in submucosal serous glandular epithelium of a bronchus; scale bar, 50 μm. (E) Margination and adhesion of neutrophils to endothelial cells of a pulmonary arteriole; scale bar, 20 μm. (G) Influenza viral antigen in epithelium of a primary bronchiole; scale bar, 50 μm. (H) Viral antigen commonly in macrophages and alveolar epithelial cells; scale bar, 20 μm. (**I**) NY18 virus; severe diffuse alveolitis with accompanying necrotizing bronchiolitis; scale bar, 50 μm. (**J**) AV18 virus; diffuse severe alveolitis and edema with necrotizing bronchiolitis; scale bar, 50 μm. (**K**) Tx/91 virus; normal alveoli; scale bar, 15 μm. (**L**) Dk/Alb virus, purulent bronchiolitis (p) with peribronchiolar mixed cell inflammation and associated moderate alveolitis (a); scale bar, 50 μm. (**M**) Dk/Alb viral antigen in bronchial epithelium; scale bar, 30 μm.

human tracheal epithelial cells expressing high amounts of terminal α2,6 SA motifs and, simultaneously, in an improved ability to overcome the inhibitory effects of human bronchial mucins associated with α2,3 SA receptors (*28*). However, mutations that caused a shift from the avian-type to human-type receptor binding specificity for the H1 subtype do not cause an equivalent shift in specificity for the H5 subtype (*24*). Likewise, the amino acid changes required to alter the H3 HA from an avian- to human-type receptor binding specificity are different from those required for the H1 HA. Therefore, it is likely that different avian HA subtypes have different structural requirements to confer receptor specificity. Thus, it is currently unknown which additional mutations in the H5 HA would cause a shift to the human-type specificity, which may be required for H5N1 viruses to transmit efficiently among humans.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 and S2
References

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Protein Kinase C β and Prolyl Isomerase 1 Regulate Mitochondrial Effects of the Life-Span Determinant p66^{Shc}

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The 66-kilodalton isoform of the growth factor adapter Shc (p66^{Shc}) translates oxidative damage into cell death by acting as reactive oxygen species (ROS) producer within mitochondria. However, the signaling link between cellular stress and mitochondrial proapoptotic activity of p66^{Shc} was not known. We demonstrate that protein kinase C β, activated by oxidative conditions in the cell, induces phosphorylation of p66^{Shc} and triggers mitochondrial accumulation of the protein after it is recognized by the prolyl isomerase Pin1. Once imported, p66^{Shc} causes alterations of mitochondrial Ca^{2+} responses and three-dimensional structure, thus inducing apoptosis. These data identify a signaling route that activates an apoptotic inducer shortening the life span and could be a potential target of pharmacological approaches to inhibit aging.

The protein p66^{Shc} (*1*–*4*) is an alternatively spliced isoform of a growth factor adapter that is phosphorylated upon oxidative stress (*2*). Ablation of the p66^{Shc} gene causes life-span prolongation with no pathological consequence (*2*). A fraction of p66^{Shc} localizes to mitochondria (*3*–*5*), where it binds to cytochrome c and acts as oxidoreductase, generating reactive oxygen species (ROS) and leading to organelle dysfunction and cell death (*5*). The route leading to p66^{Shc} activation is still unclear. Phosphorylation of a critical serine (Ser^{36}) is necessary (*2*), but the kinase responsible has not been identified. Moreover, mitochondrial p66^{Shc} is unphosphorylated, indicating that additional regulatory elements must exist.

Mitochondria receive, under stimulation by physiological agonists or toxic agents, Ca^{2+}-mediated inputs (*6*–*8*) that are decoded into effects as diverse as metabolic stimulation and apoptosis (*9*). Ca^{2+} responsiveness is a highly sensitive readout of mitochondrial state: Partial defects in mitochondrial energization, as in mitochondrial diseases, cause defects in Ca^{2+} handling by the organelle (*10*). Moreover, mitochondrial Ca^{2+} uptake is modulated by regulatory proteins such as kinases. Some protein kinase C (PKC) isoforms (*11*) specifically affect the responses of mitochondrial Ca^{2+} to agonists (PKCβ reduces them, whereas PKCζ enhances them) (*12*). PKCs are also proposed to be activated in conditions of oxidative stress (*13*). We therefore used aequorin to monitor cellular concentrations of Ca^{2+}, a green fluorescent protein with mitochondrial presequence (mtGFP) to monitor organelle structure, and other molecular tools to clarify the signaling route linking the oxidative challenge to the activation of p66^{Shc} proapoptotic effect within

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mitochondria in mouse embryonic fibroblasts (MEFs) (*14*).

Using an aequorin probe targeted by a mitochondrial presequence (mtAEQ) (*15*), we investigated organelle Ca^{2+} responses to adenosine triphosphate (ATP), an extracellular agonist that causes the release of Ca^{2+} from the endoplasmic reticulum. $p66^{Shc-/-}$ and wild-type MEFs showed similar responses of $[Ca^{2+}]_m$ to ATP, both in amplitude and in kinetics (Fig. 1, A and B). This reflects a close similarity in the global Ca^{2+} signaling patterns. Indeed, the monitoring of concentration of free cytosolic Ca^{2+} ($[Ca^{2+}]_c$) showed that the $[Ca^{2+}]_c$ rises evoked by ATP in $p66^{Shc-/-}$ and wild-type MEFs were virtually superimposable (Fig. 1, A and B, insets).

To investigate the effect of an oxidative challenge, we treated cells for 30 min before the application of ATP with various concentrations of H_2O_2. Reduction of mitochondrial Ca^{2+} responses and fragmentation of the three-dimensional mitochondrial network (*16*) was observed in wild-type MEFs (Fig. 1, A and a) several hours before signs of apoptosis (cell shrinkage and nuclear condensation, for example) were detected (fig. S1), whereas minor changes in the Ca^{2+} response and morphology were detected in $p66^{Shc-/-}$ MEFs (Fig. 1, B and b). This alteration in Ca^{2+} response was characteristically mitochondrial, because no difference in the ATP-dependent $[Ca^{2+}]_c$ rise was detected between $p66^{Shc-/-}$ and wild-type H_2O_2-treated MEFs (Fig. 1, A and B, insets). The reintroduction of $p66^{Shc}$ reestablished sensitivity to H_2O_2 in $p66^{Shc-/-}$ MEFs (Figs. 1C-c).

Production of ROS by $p66^{Shc}$ (*5*) influences the opening of the mitochondrial permeability transition pore (PTP) (*17*). We thus investigated whether the Ca^{2+} and morphology changes triggered by H_2O_2 could be prevented by the PTP blocker cyclosporine A (CsA). In CsA-treated wild-type MEFs, the rise in $[Ca^{2+}]_m$ evoked by ATP stimulation in the presence of H_2O_2 was largely restored (Fig. 2A) and the integrity of the mitochondrial network was preserved (Fig. 2a). On the contrary, no effect of CsA on $p66^{Shc-/-}$ (Fig. 2A, inset) or on MEFs not treated with H_2O_2 (fig. S2, A and B) was detected. Similar results were obtained with bongkrekic acid, another PTP inhibitor (fig. S2, C and c). Mitochondrial Ca^{2+} responses and morphology were not modified by H_2O_2 application to $p66^{Shc-/-}$ MEFs in which either the $p66^{Shc}$E132Q-E133Q mutant ($p66^{Shc}$qq), incapable of binding cytochrome c (*5*) (Fig. 2, B and b), or the $p66^{Shc}$S36A mutant (*2*) (Fig. 2, C and c) had been reintroduced, indicating that both the oxidoreductase activity of $p66^{Shc}$ and the phosphorylation of Ser^{36} are essential for the H_2O_2-induced proapoptotic changes.

Overexpression of the PKC isoform β reduces transient changes in $[Ca^{2+}]_m$ in HeLa (*12*), and PKCβ is expressed in MEF cells (fig. S3A). After application of H_2O_2, membrane staining of GFP-tagged PKCβ was detected by fluorescence microscopy (fig. S4A), showing its activation (*13*). Phosphorylated $p66^{Shc}$ was detected after treatment of cells with H_2O_2 or with 12-*O*-tetradecanoylphorbol 13-acetate (TPA), a PKC activator (Fig. 3A) (*14*). Hispidin, a specific blocker of the PKCβ isoform (fig. S4B) (*18*), inhibited $p66^{Shc}$ phosphorylation in both conditions (Fig. 3A).

Overexpression of PKCβ mimicked the activation of the endogenous kinase by oxidative

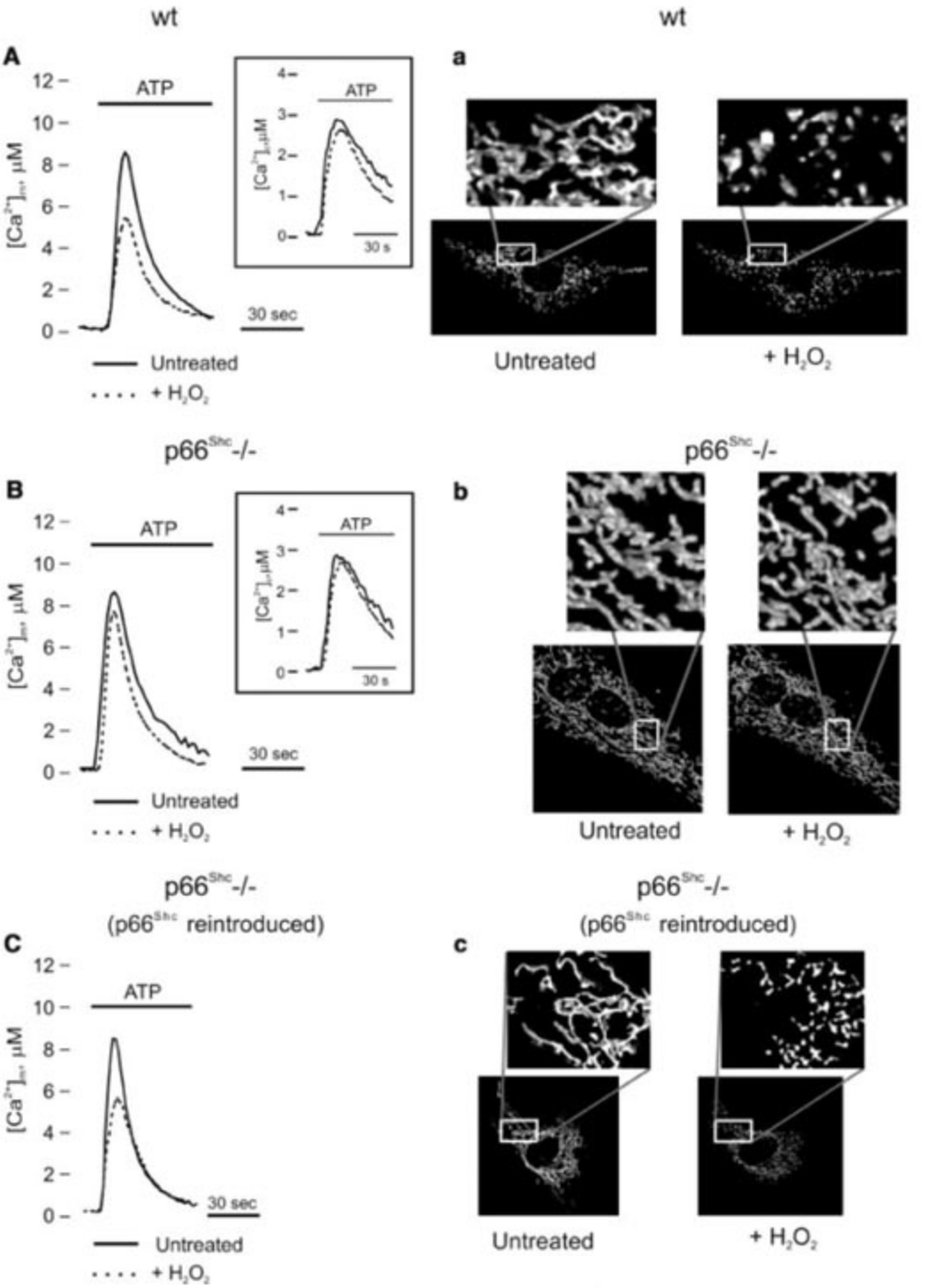

Fig. 1. Mitochondrial morphology and Ca^{2+} responses in $p66^{Shc}$ MEFs during oxidative stress. Mitochondrial and cytosolic (inset) Ca^{2+} homeostasis in wild-type (wt) (**A**) and $p66^{Shc-/-}$ (**B**) MEFs. Where indicated, mitochondrially targeted aequorin (mtAEQ)–transfected cells were treated with 100 μM ATP. wt: mitochondrial calcium concentration ($[Ca^{2+}]_m$) peak, 8.64 ± 0.32 μM; cytosolic calcium concentration ($[Ca^{2+}]_c$) peak, 2.90 ± 0.11 μM. $p66^{Shc-/-}$: $[Ca^{2+}]_m$ peak, 8.71 ± 0.37 μM; $[Ca^{2+}]_c$ peak, 2.91 ± 0.15 μM. Aequorin reconstitution and conversion of luminescence into $[Ca^{2+}]$ is described in (*14*). The dotted traces show the effect of treatment with H_2O_2 (1 mM, 30 min) on the ATP-dependent responses. wt: $[Ca^{2+}]_m$ peak, 5.84 ± 0.28 μM; $[Ca^{2+}]_c$ peak, 2.60 ± 0.07 μM. $p66^{Shc-/-}$: $[Ca^{2+}]_m$ peak, 7.87 ± 0.33 μM; $[Ca^{2+}]_c$ peak, 2.7 ± 0.09 μM. (**a** and **b**) Analysis of mitochondrial structure in cells treated with or without H_2O_2 (1 mM, 30 min) (a greater magnification is presented in the insets). (**C** and **c**) Reintroduced $p66^{Shc}$ reestablishes the $[Ca^{2+}]_m$ and morphology sensitivity to H_2O_2 in $p66^{Shc-/-}$ MEFs. $[Ca^{2+}]_m$ peak, 8.69 ± 0.51 μM; after H_2O_2, $[Ca^{2+}]_m$ peak, 5.76 ± 0.44 μM, $P < 0.01$. For all the experiments presented, $n \geq 15$.

challenges, causing a reduction in $[Ca^{2+}]_m$ responses in wild-type MEFs (in which the putative downstream effector is present) but not in $p66^{Shc-/-}$ MEFs (Fig. 3B). This effect was specific for PKCβ. When other isoforms were expressed (PKCα, PKCδ, PKCε, or PKCζ), the $p66^{Shc}$-dependent mitochondrial Ca^{2+} alteration was not observed (fig. S3). Moreover, when PKCβ was inhibited pharmacologically with hispidin (Fig. 3C) or its abundance was decreased with RNA interference (RNAi) (Fig. 3D), the $[Ca^{2+}]_m$ peak was minimally affected by the application of H_2O_2. Similarly, hispidin treatment preserved mitochondrial morphology (Fig. 3E).

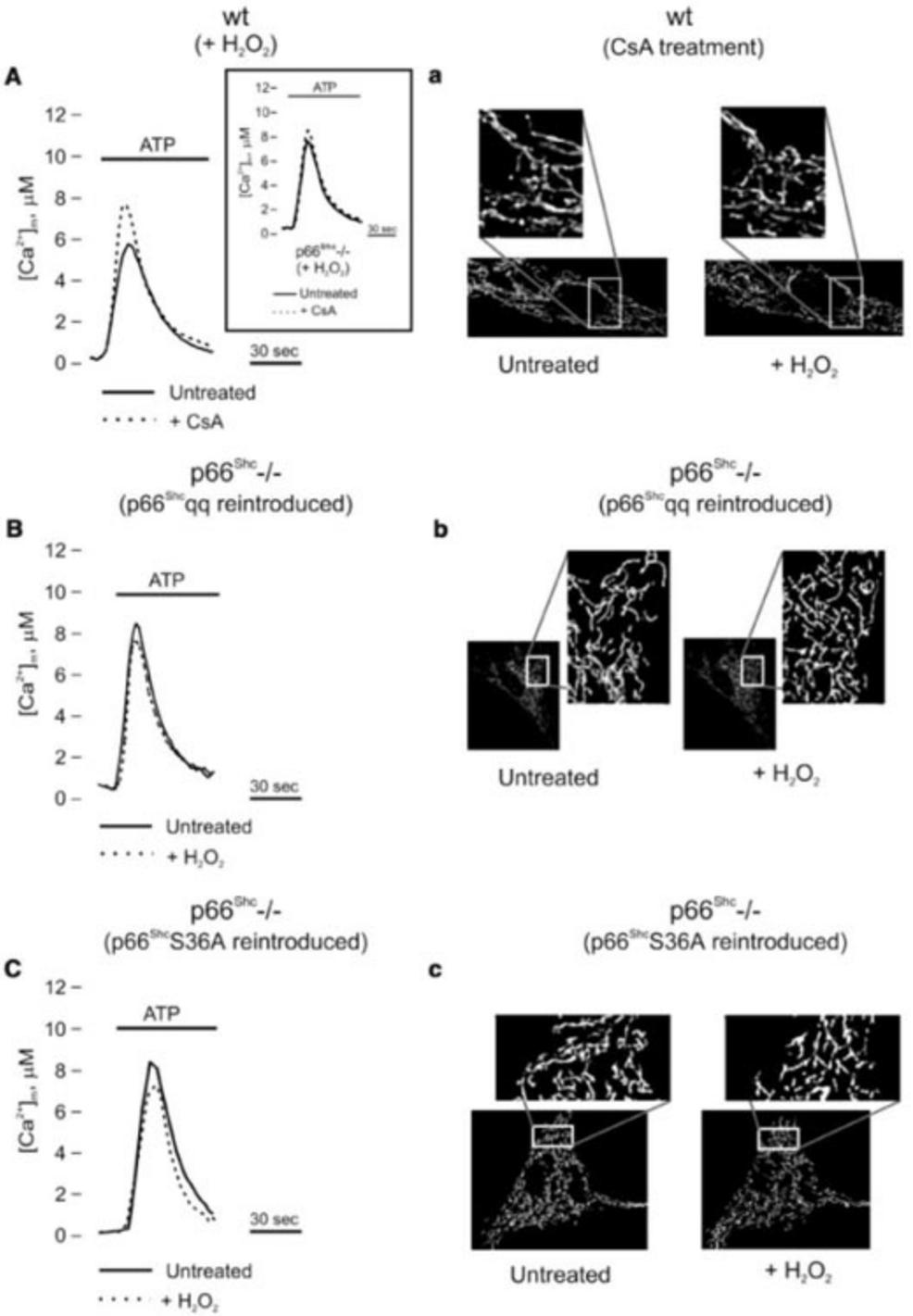

Fig. 2. Involvement of PTP, $p66^{Shc}$ binding to cytochrome c, and $p66^{Shc}$ phosphorylation in mitochondrial $p66^{Shc}$ action. (**A**) Effect of treatment with CsA (4 μM, 10 min) on H_2O_2-dependent reduction of $[Ca^{2+}]_m$ responses in wt MEFs. $[Ca^{2+}]_m$ peak, 5.84 ± 0.28 μM in cells treated only with H_2O_2; 7.58 ± 0.33 μM, $P < 0.01$, in cells pretreated with CsA, then treated with H_2O_2. No effect of CsA on $p66^{Shc-/-}$ cells was detected. $[Ca^{2+}]_m$ peak, 7.87 ± 0.33 μM in cells treated only with H_2O_2; 8.43 ± 0.54 μM in cells pretreated with CsA, then treated with H_2O_2 (Fig. 2A, inset). (**B** and **C**) Failure of the $p66^{Shc}$qq mutant ($[Ca^{2+}]_m$ peak: control, 8.35 ± 0.71 μM; H_2O_2, 7.76 ± 0.35 μM) (B) or the $p66^{Shc}$S36A mutant ($[Ca^{2+}]_m$ peak control, 8.58 ± 0.61 μM; H_2O_2, 7.74 ± 0.64 μM) (C) to reestablish mitochondrial $[Ca^{2+}]$ sensitivity to H_2O_2 in $p66^{Shc-/-}$ MEFs. All conditions as in Fig. 1. (**a** to **c**) Morphology of H_2O_2-treated, CsA-pretreated cells (a) or H_2O_2-treated cells expressing the $p66^{Shc}$qq (b) or $p66^{Shc}$S36A mutants (c).

We verified whether PKCβ inhibition reduced the apoptotic efficacy of H_2O_2 treatment. We measured cell viability 8 hours after the addition of 1 mM H_2O_2 by counting surviving cells on the microscopy stage. Hispidin caused no change in cell viability in wild-type cells but increased the number of cells surviving oxidative stress (29% ± 2.1 in H_2O_2-treated cells versus 60% ± 4.75 in hispidin pretreated cells, expressed as a percentage of the cells counted on a coverslip not exposed to H_2O_2) (fig. S5A).

To partially mimic an "aging" event, we analyzed mitochondrial Ca^{2+} responses in MEFs maintained in culture for 20 passages. In wild-type MEFs, the $[Ca^{2+}]_m$ responses gradually decreased with time in culture, whereas no alteration was observed in $p66^{Shc-/-}$ MEFs or in wild-type MEFs if the culture medium was supplemented with hispidin (fig. S5B). We also analyzed the effect of PKCβ on other mitochondrial parameters: mitochondrial membrane potential ($\Delta\Psi$) and production of ROS (*14*). PKCβ activation by TPA caused a gradual reduction in $\Delta\Psi$ in wild-type but not in $p66^{Shc-/-}$ MEFs (Fig. 3F and fig. S5C) (*4*). An increase in ROS production was observed shortly after infection of cells with an adenoviral vector driving PKCβ expression: dihydroethidium fluorescence intensity (arbitrary units) 17.70 ± 1.2 versus 14.97 ± 1.3 in nontransduced cells, supporting the view that PKCβ triggers the oxidoreductase activity of $p66^{Shc}$.

We suspected that a possible link between PKC-dependent phosphorylation of $p66^{Shc}$ and its mitochondrial oxidoreductase activity was that phosphorylation mediated transfer of $p66^{Shc}$ from the cytosol to mitochondria. The prolyl isomerase Pin1 recognizes and induces cis-trans isomerization of pSer-Pro (or pThr-Pro) bonds, conferring phosphorylation-dependent conformational changes relevant for protein function (*19*, *20*). Moreover, $Pin1^{-/-}$ MEFs are impaired in apoptosis after exposure to ultraviolet (UVc) radiation (*21*). We identified a putative consensus for Pin1 binding (Ser^{36}/Pro^{37}) in $p66^{Shc}$. Pull-down experiments (*14*) with Pin1 linked to glutathione *S*-transferase (GST-Pin1) showed that Pin1 bound to $p66^{Shc}$ after exposure of cells to UVc radiation that caused phosphorylation of $p66^{Shc}$. This interaction appeared to be phosphorylation dependent because it was reduced by treatment of cell extracts with calf intestinal phosphatase (CIP). Furthermore, the nonphosphorylatable mutant $p66^{Shc}$S36A did not show detectable binding to Pin1 (Fig. 4A).

We investigated the mitochondrial effects of H_2O_2 treatment in $Pin1^{-/-}$ MEFs. In $Pin1^{-/-}$ cells, the H_2O_2-dependent reduction of the $[Ca^{2+}]_m$ peak was smaller than that of wild-type MEFs (Fig. 4B). Similarly, in $Pin1^{-/-}$ MEFs, morphological changes caused by H_2O_2 were

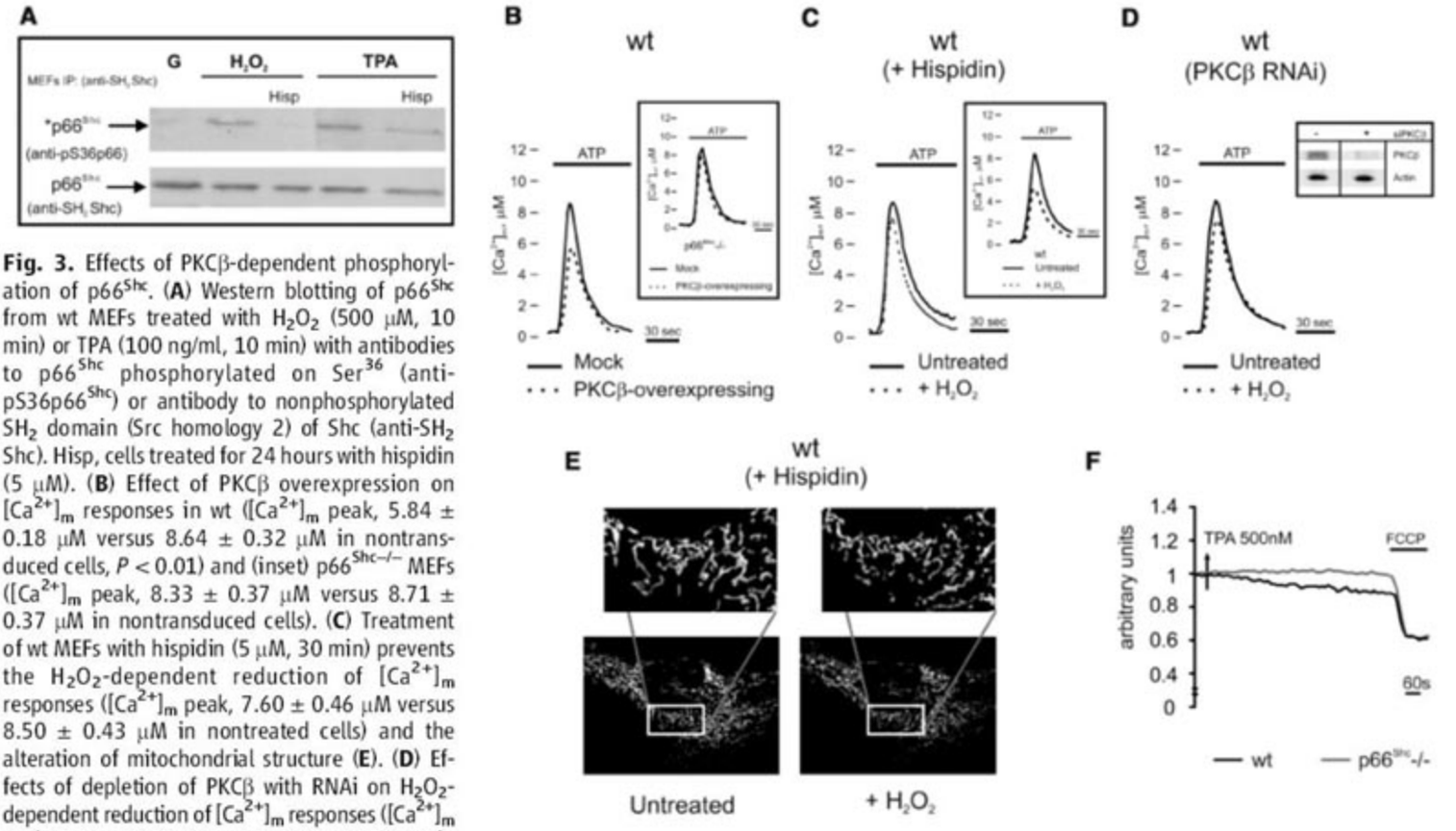

Fig. 3. Effects of PKCβ-dependent phosphorylation of $p66^{Shc}$. (**A**) Western blotting of $p66^{Shc}$ from wt MEFs treated with H_2O_2 (500 μM, 10 min) or TPA (100 ng/ml, 10 min) with antibodies to $p66^{Shc}$ phosphorylated on Ser^{36} (anti-pS36p66^{Shc}) or antibody to nonphosphorylated SH_2 domain (Src homology 2) of Shc (anti-SH_2 Shc). Hisp, cells treated for 24 hours with hispidin (5 μM). (**B**) Effect of PKCβ overexpression on $[Ca^{2+}]_m$ responses in wt ($[Ca^{2+}]_m$ peak, 5.84 ± 0.18 μM versus 8.64 ± 0.32 μM in nontransduced cells, $P < 0.01$) and (inset) $p66^{Shc-/-}$ MEFs ($[Ca^{2+}]_m$ peak, 8.33 ± 0.37 μM versus 8.71 ± 0.37 μM in nontransduced cells). (**C**) Treatment of wt MEFs with hispidin (5 μM, 30 min) prevents the H_2O_2-dependent reduction of $[Ca^{2+}]_m$ responses ($[Ca^{2+}]_m$ peak, 7.60 ± 0.46 μM versus 8.50 ± 0.43 μM in nontreated cells) and the alteration of mitochondrial structure (**E**). (**D**) Effects of depletion of PKCβ with RNAi on H_2O_2-dependent reduction of $[Ca^{2+}]_m$ responses ($[Ca^{2+}]_m$ peak, 7.43 ± 0.49 μM versus 8.81 ± 0.56 μM in nontreated cells). All conditions as in Fig. 1. Expression of PKCβ after silencing is shown in the Western blot (inset). (**F**) Kinetics of tetramethyl rhodamine methyl ester (TMRM) fluorescence of wt and $p66^{Shc-/-}$ cells treated with TPA. FCCP (carbonyl cyanide p-trifluoromethoxyphenylhydrazone), an uncoupler of oxidative phosphorylation, completely collapses the $\Delta\Psi$. The traces are representative of single cell responses.

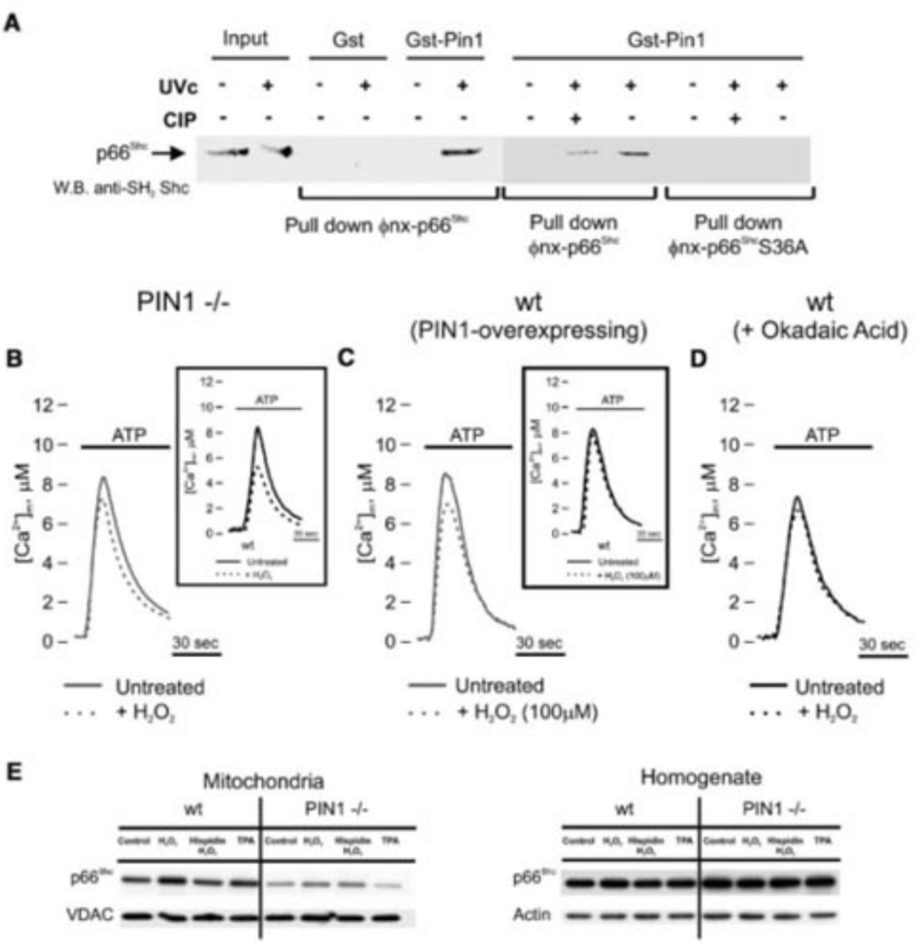

Fig. 4. Pin1 induces $p66^{Shc}$ mitochondrial translocation after Ser^{36} phosphorylation. (**A**) Total lysates from Phoenix cells (Φnx) transfected with $p66^{Shc}$ or its S36A mutant, UV-irradiated and/or treated with CIP, were subjected to GST or GST-Pin1 pull-down followed by immunoblotting with antibody to Shc. (**B**) Effect of H_2O_2 on the ATP-dependent $[Ca^{2+}]_m$ responses in $Pin1^{-/-}$ ($[Ca^{2+}]_m$ peak, 8.64 ± 0.49 μM in control versus 6.98 ± 0.46 μM in H_2O_2 treated) and (inset) wt ($[Ca^{2+}]_m$ peak, 8.41 ± 0.22 μM in control versus 5.02 ± 0.39 μM, $P < 0.01$ in H_2O_2 treated) MEFs. (**C**) Effect of 100 μM H_2O_2 on $[Ca^{2+}]_m$ responses in Pin1 overexpressing MEFs ($[Ca^{2+}]_m$ peak, 8.60 ± 0.58 μM in control versus 7.26 ± 0.26 μM H_2O_2 treated, $P < 0.05$) and (inset) in wt MEFs ($[Ca^{2+}]_m$ peak, 8.64 ± 0.49 μM in control versus 8.56 ± 0.31 μM, H_2O_2 treated). (**D**) Effects of okadaic acid (1 μM, 1 hour) on H_2O_2-dependent reduction of $[Ca^{2+}]_m$ responses ($[Ca^{2+}]_m$ peak, 7.58 ± 0.33 μM versus 6.83 ± 0.24 μM, in okadaic acid pretreated cells before and after H_2O_2 treatment, respectively). All conditions as in Fig. 1. (**E**) Western blot of $p66^{Shc}$ protein levels in the mitochondrial fraction and in the cell homogenate from wt and $Pin1^{-/-}$ MEFs.

minimal (fig. S6A). Overexpression of Pin1 sensitized cells to weaker oxidative stress. When wild-type MEFs were subjected to mild oxidative stress (100 μM H_2O_2 for 15 min instead of 1 mM for 30 min), no alteration in the agonist-dependent $[Ca^{2+}]_m$ transient was detected, whereas in Pin1 overexpressing cells, the peak was reduced (Fig. 4C). In certain substrates, the phosphoserine-proline (phosphoS-P) sites, once isomerized by Pin1, are recognized and dephosphorylated by PP2A (*20*). In cells treated with okadaic acid (PP2A inhibitor), the reduction in agonist-dependent $[Ca^{2+}]_m$ responses was markedly smaller (Fig. 4D) than that in wild-type cells, which might suggest that dephosphorylation by PP2A follows Pin1 recognition and is necessary for the mitochondrial effects of $p66^{Shc}$.

Finally, we tested the hypothesis that Pin1-dependent isomerization of $p66^{Shc}$ enhances the transfer of the protein to the organelle. We evaluated the mitochondrial pool of $p66^{Shc}$ in wild-type and $Pin1^{-/-}$ MEFs by subcellular fractionation and immunoblotting (Fig. 4E and fig. S6B) (*14*). In wild-type cells, oxidative stress increased the amount of $p66^{Shc}$ within mitochondria (~+100%). This effect appeared to depend on PKC activity, because a similar increase was evoked by treatment of cells with TPA, and hispidin inhibited the effects of H_2O_2 treatment. Blots of total homogenate showed only a small increase in the total amount of $p66^{Shc}$ (~+15%) (*4*), indicating that there was net translocation of $p66^{Shc}$ to the organelle. In $Pin1^{-/-}$ MEFs, the mitochondrial fraction of $p66^{Shc}$ was smaller, both at rest or after treatment with H_2O_2 or TPA. TPA had no detectable effect on localization of $p66^{Shc}$ in the $Pin1^{-/-}$ cells.

Overall, these data highlight a molecular route that links an oxidative challenge to the activation of $p66^{Shc}$ and the recruitment of mitochondria in apoptosis and may contribute to the aging properties of this protein.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/659/DC1
Materials and Methods
Figs. S1 to S6
References

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Targeting of Diacylglycerol Degradation to M1 Muscarinic Receptors by β-Arrestins

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Seven-transmembrane receptor (7TMR) signaling is transduced by second messengers such as diacylglycerol (DAG) generated in response to the heterotrimeric guanine nucleotide–binding protein G_q and is terminated by receptor desensitization and degradation of the second messengers. We show that β-arrestins coordinate both processes for the G_q-coupled M1 muscarinic receptor. β-Arrestins physically interact with diacylglycerol kinases (DGKs), enzymes that degrade DAG. Moreover, β-arrestins are essential for conversion of DAG to phosphatidic acid after agonist stimulation, and this activity requires recruitment of the β-arrestin–DGK complex to activated 7TMRs. The dual function of β-arrestins, limiting production of diacylglycerol (by receptor desensitization) while enhancing its rate of degradation, is analogous to their ability to recruit adenosine 3′,5′-monophosphate phosphodiesterases to G_s-coupled β_2-adrenergic receptors. Thus, β-arrestins can serve similar regulatory functions for disparate classes of 7TMRs through structurally dissimilar enzymes that degrade chemically distinct second messengers.

Stimulation of 7TMRs activates heterotrimeric guanine nucleotide–binding proteins (G proteins), initiating the production of second messenger molecules. For 7TMRs coupled to the G protein family member G_s, activation of adenylyl cyclase increases intracellular adenosine 3′,5′-monophosphate (cAMP) concentrations; 7TMRs that couple to $G_{q/11}$ stimulate phospholipase C and consequent hydrolysis of phosphatidylinositol 4,5-bisphosphate to produce inositol 1,4,5-trisphosphate and diacylglycerol (DAG) (*1*). Proper regulation of signal transduction requires G protein inactivation, degradation of second messengers, and silencing of activated receptors (desensitization) to return the cell to a basal state. Deactivation of G proteins is achieved through the intrinsic guanosine triphosphatase (GTPase) activity of the α subunit with subsequent reassembly of the inactive heterotrimeric complex. However, unlike the autocatalytic G proteins, most second messenger molecules require specific enzymes for metabolism to an inactive form. For DAG, regulation is particularly crucial because dysregulation leading to prolonged DAG signaling is tumorigenic (*2*, *3*).

The main pathway of DAG metabolism is phosphorylation by members of the family of diacylglycerol kinases (DGKs) (*4*). DGKs are predominantly cytoplasmic and translocate to the plasma membrane upon stimulation of many receptors, including 7TMRs. These enzymes catalyze the adenosine triphosphate (ATP)–dependent creation of phosphatidic acid (PA) through phosphorylation of the *sn*-3 position of DAG, thus negatively regulating DAG-dependent proteins such as protein kinase C (PKC). However, PA itself is a signaling molecule that influences vesicle trafficking (*5*), promotes translocation of the protein kinase Raf to the plasma membrane (*6*), and affects the activity of multiple enzymes, including type I phosphatidylinositol 5-kinases (*7*, *8*), PKCζ (*9*), and small GTPase proteins (*10*).

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Homologous desensitization of 7TMRs occurs through a highly conserved mechanism. The phosphorylation of cytoplasmic 7TMR serine and threonine residues by G protein–coupled receptor kinases promotes the translocation and binding of β-arrestin proteins, sterically hindering receptor–G protein coupling and diminishing G protein signaling (*11*). β-Arrestins interacting with AP-2 (*12*) and clathrin (*13*) then internalize activated receptors from the cell surface via clathrin-coated pits. β-Arrestins also recruit PDE4 phosphodiesterases to stimulated β_2-adrenergic receptors, thereby accelerating the rate of cAMP degradation in a concerted mechanism of receptor desensitization and second messenger inactivation (*14*). Here, we investigated whether β-arrestins might function more generally to coordinate second messenger inactivation and assist DGKs to quench DAG signaling.

To test whether β-arrestins interact with DGKs, we transiently overexpressed hemagglutinin (HA) epitope–tagged DGK α, β, γ, δ, ε, ζ, or ι in COS7 cells along with FLAG epitope–tagged β-arrestin 1, β-arrestin 2, or pcDNA3 vector (Fig. 1A). Overnight incubation of cell lysates with resin coated with antibody to the FLAG epitope revealed coimmunoprecipitation of all seven HA-tagged DGKs with FLAG-tagged β-arrestin 1 and β-arrestin 2, but not with vector controls (Fig. 1A). Coimmunoprecipitation of endogenous β-arrestin 1 and 2 with HA-DGKζ verified this interaction (Fig. 1B). Stimulation of endogenous M1 receptors (M1R) with carbachol (50 μM) or direct stimulation of PKC with 100 nM phorbol ester had no effect on the amount of β-arrestin immunoprecipitated, which indicates

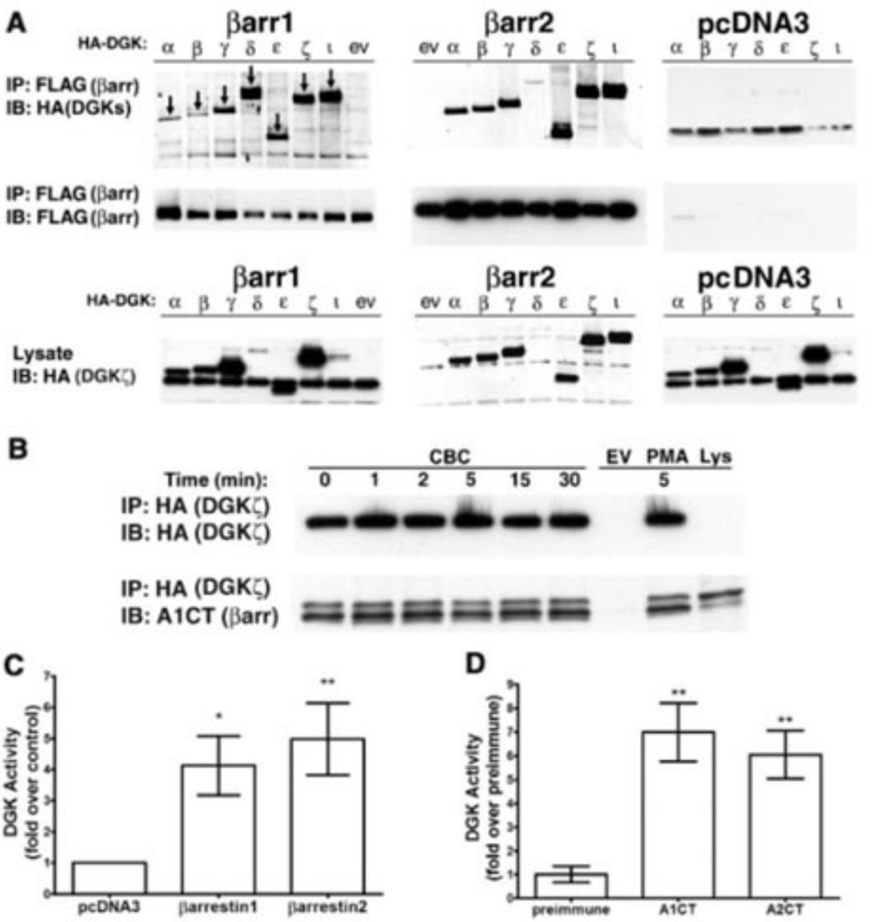

Fig. 1. Coimmunoprecipitation of DGK isoforms and DAG kinase activity with β-arrestins. (**A**) Top and middle: Western blots of FLAG immunoprecipitates from COS7 cells overexpressing HA-tagged DGK isoforms cotransfected with FLAG β-arrestin 1 (βarr1), FLAG β-arrestin 2 (βarr2), or pcDNA3 vector. Bottom: Cell lysate immunoblots normalized for total protein, confirming construct expression. Images are representative of five independent experiments. (**B**) Western blots of immunoprecipitated HA-DGKζ (top) and coimmunoprecipitated endogenous β-arrestins (bottom) after stimulation with 50 μM carbachol or 1 μM phorbol ester, as indicated. Data are representative of three independent experiments (ev, empty vector; PMA, phorbol 12-myristate 13-acetate; Lys, HEK293 cell lysate). (**C**) In vitro DAG kinase assays were performed on FLAG–β-arrestin immunocomplexes as described (*15*). Data were normalized to empty vector transfections and represent the mean ± SE of four independent experiments. (**D**) Endogenous β-arrestins were immunoprecipitated with rabbit polyclonal antibodies A1CT or A2CT and analyzed as above. Data were normalized versus preimmune rabbit antiserum and represent the mean ± SE of five independent experiments. Statistical significance was determined by repeated-measures analysis of varriance (ANOVA) with a Bonferroni post hoc test to correct for multiple comparisons ($^*P < 0.05$, $^{**}P < 0.01$).

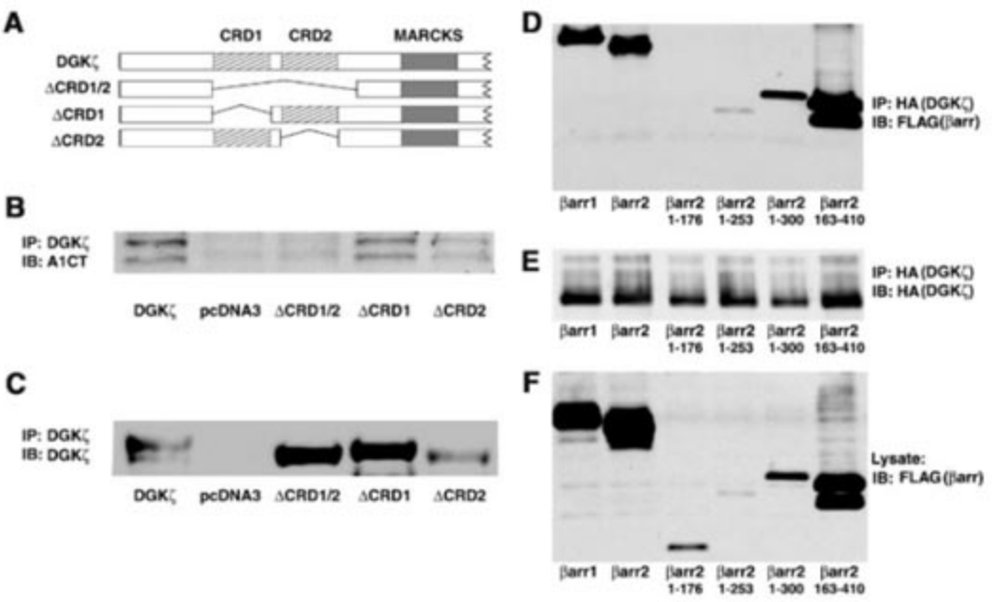

Fig. 2. Interaction of β-arrestins with the cysteine-rich domains of DGKζ. (**A**) Diagram showing truncation sites of the DGKζ deletion mutants. CRD, cysteine-rich domain; MARCKS, myristoylated alanine-rich C-kinase substrate domain. (**B**) A1CT blot of endogenous β-arrestins immunoprecipitated with DGKζ mutants. (**C**) The same immunoblot reprobed with antibody to DGKζ (*15*). (**D**) Western blot of β-arrestin 2 truncation mutants coimmunoprecipitated with HA-DGKζ. (**E**) Anti-HA probe of HA-DGKζ samples confirming comparable protein immunoprecipitation. (**F**) Expression levels of FLAG-tagged β-arrestin 2 mutants in HEK293 cell lysates. All panels are representative of at least four independent experiments.

that β-arrestins and DGKs can exist in a constitutively formed protein complex.

To examine the activity of β-arrestin–bound DGKs, we transiently transfected FLAG–β-arrestins and HA-DGKζ into human embryonic kidney HEK293 cells and tested FLAG immunoprecipitates for DAG kinase activity in vitro (*15*). The two β-arrestin isoforms were associated with similar amounts of DGK enzymatic activity (Fig. 1C). Endogenous β-arrestins immunoprecipitated with rabbit polyclonal antibodies to β-arrestin 1 and 2 [A1CT (*16*) and A2CT (*16*)] also showed significantly more associated endogenous DGK activity than did controls (Fig. 1D).

To map the site of β-arrestin binding to DGKs, we used a panel of DGKζ deletion mutants (*17*) to immunoprecipitate endogenous β-arrestins from HEK293 cells. Preliminary mapping implicated the N terminus in β-arrestin binding (fig. S1), and finer mapping of this region showed a requirement for the cysteine-rich domains (CRDs) in this interaction (Fig. 2, A to C). This agrees with our data showing that β-arrestin interacts with multiple DGKs, as the CRDs are one of two elements conserved across the entire DGK family (the catalytic domain being the other). The CRDs are necessary for the translocation of DGKζ (*18*), and although DAG does not induce DGK translocation, receptor stimulation induces robust membrane recruitment (*19*); these observations are consistent with β-arrestin–mediated DGK trafficking.

The critical regions of β-arrestin required for DGKζ binding were determined using a similar approach with multiple β-arrestin 2 truncation mutants (Fig. 2, D to F). Deletion of either the N or C terminus of β-arrestin 2 was of little consequence. However, the mutant composed of amino acids 1 to 176 was not observed in HA-DGKζ immunoprecipitates. Therefore, the critical elements of DGKζ binding within β-arrestin 2 appear to be between residues 177 and 253, corresponding to an outer loop in the C-terminal half of β-arrestin 1 and 2.

To investigate the consequences of β-arrestin–DGK complexation in cells, we quantified carbachol-induced production of phosphatidic acid by whole-cell ^{32}P labeling. Labeled lipid species were extracted from HEK293 cells transfected with pcDNA3 vector, FLAG–β-arrestin 1 or FLAG–β-arrestin 2 (Fig. 3A), then separated by thin-layer chromatography (*16*) (Fig. 3B). Quantification of ^{32}P incorporation (Fig. 3C) revealed that, relative to nonstimulated cells, vector-transfected cells produced 4.8 ± 0.4 times as much radiolabeled PA with 5 min of endogenous M1R stimulation. Overexpression of either β-arrestin 1 or β-arrestin 2 increased agonist-induced PA levels to 7.2 ± 0.6 and 8.5 ± 0.9 times the basal state, respectively.

To further analyze the role of β-arrestins in M1R stimulation of DGK activity, we used small interfering RNA (siRNA) to deplete endog-

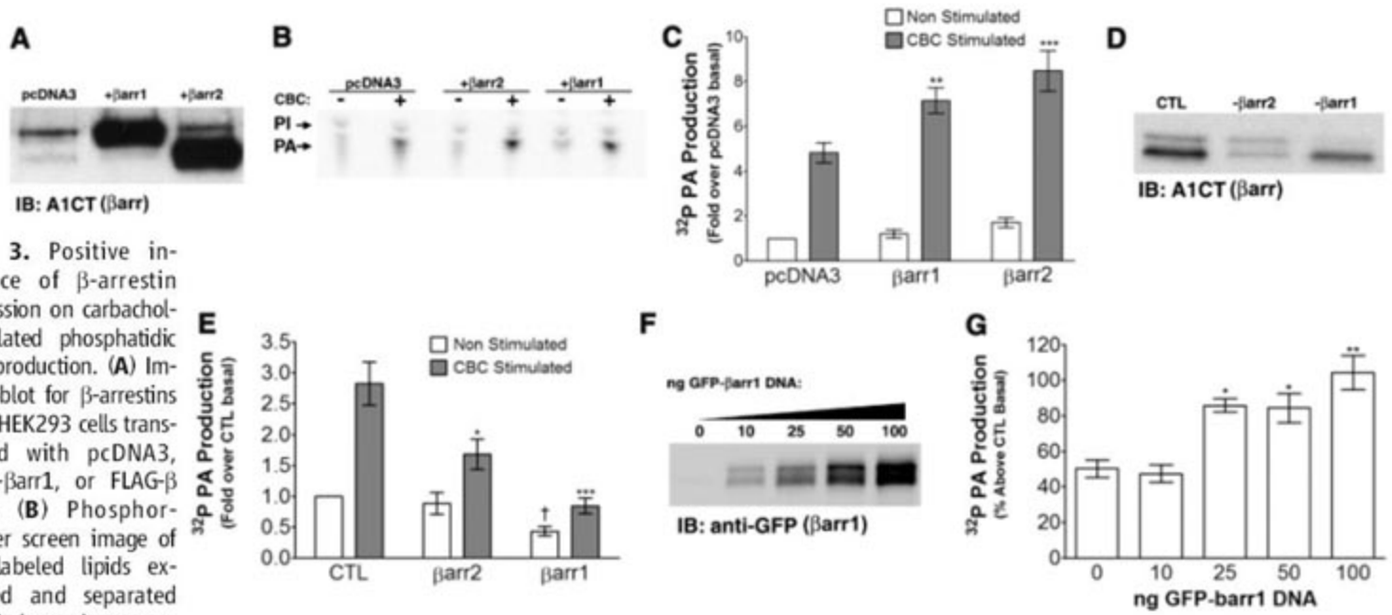

Fig. 3. Positive influence of β-arrestin expression on carbachol-stimulated phosphatidic acid production. (**A**) Immunoblot for β-arrestins from HEK293 cells transfected with pcDNA3, FLAG-βarr1, or FLAG-β arr2. (**B**) Phosphorimager screen image of radiolabeled lipids extracted and separated by thin-layer chromatography from β-arrestin– and control-transfected cells with and without 50 μM carbachol stimulation of endogenous M1Rs for 5 min (CBC, carbachol; PI, phosphatidylinositol; PA, phosphatidic acid). (**C**) Quantification of carbachol-stimulated [^{32}P]PA normalized to nonstimulated controls. Values shown represent the mean ± SE from eight independent experiments. Statistical significance was determined by one-way ANOVA with a Bonferroni post hoc test to correct for multiple comparisons (**$P < 0.01$ versus stimulated pcDNA3; ***$P < 0.001$ vs. stimulated pcDNA3). (**D**) Western blot of β-arrestins from HEK293 cells treated with β-arrestin–specific siRNA oligonucleotides. (**E**) Summary data of carbachol-stimulated [^{32}P]PA production across β-arrestin siRNA treatments. Values shown represent the mean ± SE of five independent experiments. Statistical significance was determined by one-way ANOVA with a Bonferroni post hoc test to correct for multiple comparisons (*$P < 0.05$ versus stimulated control cells; ***$P < 0.001$ versus stimulated control cells; †$P < 0.01$ versus nonstimulated control cells). (**F**) Anti-GFP immunoblot showing expression of GFP-tagged rat β-arrestin 1 in HEK293 cells treated with siRNA specific for human β-arrestin 1. (**G**) Summary data of rescued [^{32}P]PA production normalized to nonstimulated control siRNA transfections. Values shown represent the mean ± SE of three independent experiments. Statistical significance was determined by one-way ANOVA with a Bonferroni post hoc test to correct for multiple comparisons (*$P < 0.05$ versus nonstimulated cells; **$P < 0.01$ versus nonstimulated cells).

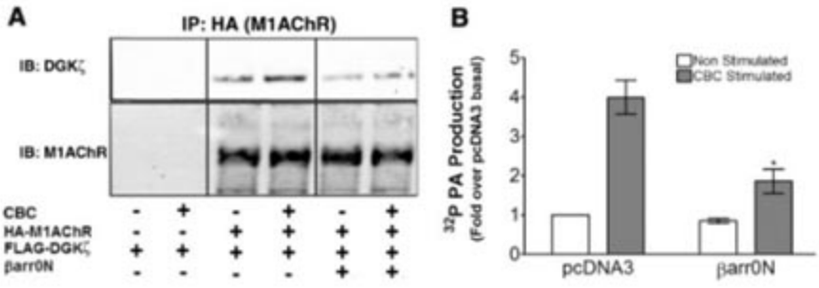

Fig. 4. Dominant negative effect of βarr0N on DGK translocation to the M1 muscarinic receptor. (**A**) Western blots of dithiobis-maleimidoethane–cross-linked HA-M1R immunoprecipitates from HEK293 cells transfected with FLAG-DGKζ and βarr0N as described, with and without 50 μM carbachol stimulation for 5 min. (**B**) Summary data of three experiments showing the effect of βarr0N overexpression on agonist-induced [^{32}P]PA production. Statistical significance was determined by a paired *t* test (*$P < 0.05$ versus stimulated pcDNA3).

enous β-arrestins in HEK293 cells (*16*). Specific siRNAs reduced expression of β-arrestin 1 by ~80% and β-arrestin 2 by ~90% (Fig. 3D) and significantly affected the [^{32}P]PA generated in response to carbachol stimulation (Fig. 3E). Relative to untreated, nonstimulated cells, cells transfected with nonsilencing control siRNA showed a factor of 2.8 ± 0.4 increase in the amount of PA produced after agonist treatment, whereas β-arrestin 2 siRNA-treated cells produced only 1.7 ± 0.2 times as much radioactive PA. The effects of depleting β-arrestin 1 were even greater, reducing basal PA concentrations to less than half (0.43 ± 0.08) of control and limiting the carbachol-stimulated response to 0.8 ± 0.1 of the control basal state.

To validate the RNA interference results, we investigated the effect of replenishing cells with exogenously expressed β-arrestin 1 after siRNA treatment. Rat β-arrestin 1 fused to green fluorescent protein (GFP) was expressed in cells transfected with siRNA targeting the human β-arrestin 1 sequence. Although β-arrestin 1 proteins from these species are 90% identical, siRNA directed against human β-arrestin 1 has no effect on expression of rat β-arrestin 1 because of six nucleotide mismatches within the 21-base sequence to which the siRNA hybridizes. With an increasing titration of rat GFP–β-arrestin 1 plasmid, there was a proportional rise in fusion protein expression (Fig. 3F) (to about 5 times the amount of endogenous β-arrestin 1) and a concomitant augmentation in the incorporation of ^{32}P into PA (Fig. 3G and fig. S2B). GFP–β-arrestin 1 rescued 71% of the carbachol-stimulated PA (100 ± 0.5% increase over basal control cells) (Fig. 3G).

Next, we sought to dissociate the roles of β-arrestins in receptor desensitization from their DGK scaffolding function. We screened the β-arrestin 2 deletion mutants used previously for use as a dominant negative protein to inhibit DGK activity. The β-arrestin 2 163–410 mutant, henceforth referred to as βarr0N (β-arrestin 2, no N terminus), was robustly overexpressed, bound all isoforms of DGK tested in coimmunoprecipitation experiments (fig. S3A), and also competed with endogenous β-arrestins for binding to DGKs in a dose-dependent manner (fig. S3B). However, this mutant lacks N-terminal residues that are critical for receptor binding (*20*) and thus, as expected, failed to interact with agonist-stimulated 7TMRs (fig. S3C). Thus, βarr0N appeared to act as a dominant negative β-arrestin, retaining DGKs in the cytoplasm and prohibiting translocation of the β-arrestin–DGK complex to activated 7TMRs. Immunoblotting muscarinic receptor immunoprecipitates for cross-linked DGKζ revealed a carbachol-dependent association that was eliminated by βarr0N overexpression (Fig. 4A and fig. S3D). We compared HEK293 cells transfected with βarr0N to cells transfected with an equal amount of pcDNA3 vector. Extracts from control cells showed a factor of 4.0 ± 0.4 increase in DAG phosphorylation after agonist stimulation, whereas the βarr0N-transfected cells generated only a factor of 1.9 ± 0.3 increase (Fig. 4B and fig. S2C).

Our results demonstrate the ability of β-arrestins to recruit DGKs to a ligand-activated G_q-coupled 7TMR. This finding is analogous to their previously discovered function in recruiting cAMP phosphodiesterases to the G_s-coupled β_2-adrenergic receptor. However, the second messenger degrading enzymes involved in the G_s and G_q pathways are structurally and functionally unrelated. Thus, the data suggest a very general role for β-arrestins in coordinating second messenger degradation as well as receptor desensitization. Unlike adenosine 5′-monophosphate (the degradative product of phosphodiesterase action on cAMP), which is biologically inactive, PA resulting from DAG phosphorylation by DGKs has been implicated as an effector in many signaling pathways. Consequently, β-arrestin–mediated targeting of DGKs to 7TMRs may also serve as a critical molecular switch, turning off DAG-dependent signaling (such as PKC) while activating PA-sensitive pathways.

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21. The β-arrestin 2 truncation mutants were created previously in the lab of R.J.L. by M. Field. We thank S. V. Naga Prasad for advice in thin-layer chromatography, D. Addison and E. Hall for excellent secretarial assistance, and D. Watters for outstanding support. Supported in part by NIH grants HL16037 and HL70631 (R.J.L.) and CA95463 (M.K.T.). R.J.L. is an Investigator with the Howard Hughes Medical Institute.

Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/663/DC1
Materials and Methods
Figs. S1 to S3

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Structural and Regulatory Genes Required to Make the Gas Dimethyl Sulfide in Bacteria

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Dimethyl sulfide (DMS) is a key compound in global sulfur and carbon cycles. DMS oxidation products cause cloud nucleation and may affect weather and climate. DMS is generated largely by bacterial catabolism of dimethylsulfoniopropionate (DMSP), a secondary metabolite made by marine algae. We demonstrate that the bacterial gene *dddD* is required for this process and that its transcription is induced by the DMSP substrate. Cloned *dddD* from the marine bacterium *Marinomonas* and from two bacterial strains that associate with higher plants, the N_2-fixing symbiont *Rhizobium* NGR234 and the root-colonizing *Burkholderia cepacia* AMMD, conferred to *Escherichia coli* the ability to make DMS from DMSP. The inferred enzymatic mechanism for DMS liberation involves an initial step in which DMSP is modified by addition of acyl coenzyme A, rather than the immediate release of DMS by a DMSP lyase, the previously suggested mechanism.

Large amounts of DMSP are produced annually by many marine phytoplankton (*1–3*), seaweed macroalgae (*4*), and some angiosperms, including the salt marsh grass *Spartina* (*5*). For these organisms, DMSP is an osmoprotectant, which is released during physiological and mechanical stress, viral lysis, or grazer attack (*6*). Much of this is then catabolized through microbial action, mostly by marine bacteria (*7–9*). DMSP catabolism is hypothesized to occur through one of two pathways (*7*, *10*). The dominant process, which carries about 80% of the total global flux, involves demethylation of DMSP (*10*). The other,

DMSP lyase, route (*7*) involves a different enzymatic cleavage of DMSP (Fig. 1) that results in DMS, the predominant form of sulfur emitted from marine environments. DMS oxidation products nucleate cloud formation, increasing the albedo over the oceans, and hence may contribute to a reduction in global temperatures (*2*). DMS is also a potent chemoattractant for some crustaceans (copepods) and birds (shearwaters and petrels) as a marker for their potential food supplies (*11*, *12*).

Recently, a gene, *dmdA*, which specifies a DMSP demethylase, was identified in *Silicibacter pomeroyi* DSS-3, a marine α-proteobacterium that can also form DMS from DMSP (*13*, *14*). Orthologs of this demethylase occur in many marine bacteria, including the abundant *Pelagibacter ubique* (*14*). No gene(s) involved in the DMSP lyase pathway are known, although several classes of bacteria grow with DMSP as the sole carbon source, releasing DMS when they do so (*7*). We term this phenotype Ddd^+ (DMSP-dependent DMS).

To identify some of the key *ddd* genes, we sampled bacteria from root surfaces of the salt marsh grass *Spartina anglica* and grew them with DMSP as the sole carbon source (*15*). We purified a DMSP-catabolizing bacterium (strain MWYL1), which had a 16S rRNA sequence 99% identical to that of *Marinomonas*, a marine γ-proteobacterium genus known to include Ddd^+ strains (*16*). Cultures of MWYL1 were grown in minimal media with either DMSP, glycerol, or both as carbon sources and assayed for DMS production. DMS was produced only if cells were pregrown with DMSP (with or without glycerol), demonstrating that DMSP pretreatment induced DMS-synthesizing activity 100-fold in *Marinomonas* (Table 1).

To clone the relevant *Marinomonas ddd* genes, we made a fosmid library of MWYL1 genomic DNA in *Escherichia coli*. No primary transfectants grew when DMSP was provided as the sole carbon source, but one *E. coli* transfectant produced DMS when grown on medium with DMSP plus glycerol. Retransformation of *E. coli* confirmed that this Ddd^+ phenotype was due to this fosmid. Through subcloning, we identified two predicted transcriptional units, termed *dddD* and *dddTBCR* (containing *dddT*, *dddB*, *dddC*, and *dddR*), which are transcribed divergently from each other (Fig. 2). These two operons, along with their promoter regions, were subcloned individually. We found that *E. coli* containing either *dddD* or *dddTBCR*, each with their native promoters, produced no DMS when grown on DMSP. Therefore, both of these operons are required for the Ddd^+ phenotype. We also cloned *dddD* into a vector (pET21a) where its expression was induced by isopropyl-β-thiogalactopyranoside (IPTG). *E. coli* containing this plasmid formed DMS (500 nmol DMS min^{-1} mg dry $weight^{-1}$) from DMSP but only upon IPTG addition. Thus, *dddD* alone confers a Ddd^+ phenotype if expressed from an ectopic promoter. The failure of *dddD* to confer a Ddd^+ phenotype when controlled by its own promoter suggested that it required a positively acting transcriptional regulator, most likely encoded by the *dddTBCR* operon. This was confirmed; in the presence of DMSP, subcloned *dddR* alone activated expression of a transcriptional fusion in which *dddD*, with its native promoter, was fused to *lacZ* (Table 2). Consistent with this, the sequence of DddR showed that it was in the LysR family of bacterial transcriptional regulators.

The sequence of the *DddD* gene product placed it in the family of type III acyl coenzyme A (CoA) transferases, not in a lyase family as hypothesized (*7*). The closest DddD homolog (26% identity) with known function is *E. coli* CaiB, a γ–butyrobetainyl-CoA:carnitine CoA-transferase that adds acyl CoA to the amino acid carnitine, a molecule with structural sim-

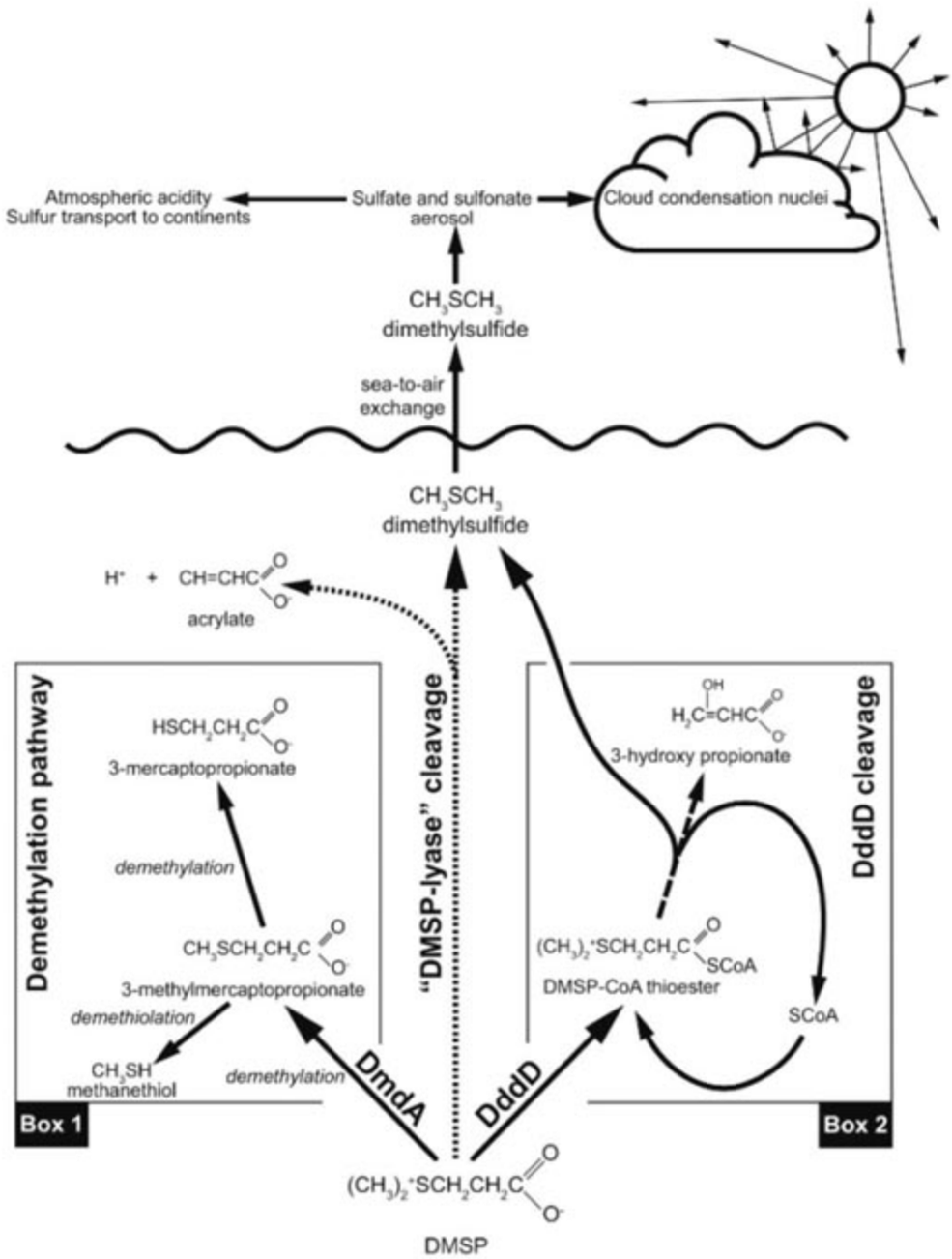

Fig. 1. Representation of conventional and revised pathways for DMSP catabolism. The dotted, central line portrays the DMSP lyase pathway. Box 1 shows the demethylation pathway, the first step being catabolized by DmdA (*14*). Box 2 shows our suggested incomplete pathway, derived from predicted general functions of DddD.

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ilarity to DMSP. The *Marinomonas* MWYL1 Ddd proteins were >93% identical to proteins in the closely related *Marinomonas* strains MED121 and HTCC2207. Furthermore, the Ddd$^+$ marine α-proteobacteria *S. pomeroyi* DSS-3 and *Sagittula stellata* E37 both have proteins with ~40% identity to DddD of *Marinomonas* (*13*) (fig. S1).

Two other bacterial strains not previously known to catabolize DMSP have proteins about 60% identical to *Marinomonas* DddD. These are the α-proteobacterial N_2-fixing, symbiotic *Rhizobium* NGR234, which induces nodules on many different legumes and on the nonlegume *Parasponia* (*17*, *18*), and the β-proteobacterium *Burkholderia cepacia* AMMD, found on roots of many angiosperms (*19*). Neither *Rhizobium* NGR234 nor *B. cepacia* AMMD grew on DMSP as sole carbon source, but both emitted DMS when grown with DMSP plus another carbon source. As with *Marinomonas*, their Ddd$^+$ phenotype was induced by DMSP (Table 1). When *dddD* homologs of *Rhizobium* NGR234 and *B. cepacia* AMMD were individually cloned and supplied by a promoter in the vector, they both conferred a Ddd$^+$ phenotype to *E. coli* (Table 1). Other strains of *Rhizobium* and *Burkholderia* that lack *dddD* (*15*) made no DMS on media containing DMSP plus glycerol.

The closest homolog to *Marinomonas* DddR was a protein of 60% identity from *B. cepacia* AMMD (Fig. 2). The cloned AMMD *dddR*-like gene, which is adjacent to *dddD* of this species, fully induced expression of *Marinomonas dddD-lacZ* in *E. coli* that was pregrown with DMSP (Table 2). Thus, *B. cepacia* DddR activates expression of *dddD* of the distantly related *Marinomonas*.

To confirm the importance of *dddD* and *dddR* in DMSP catabolism in *Marinomonas*, we made transposon insertions in each of these genes (*15*). Neither the DddD$^-$ nor the DddR$^-$ mutants grew on DMSP as the sole carbon source, and neither made DMS in DMSP plus glycerol medium (Table 1). Further, the *dddD-lacZ* fusion was not expressed in the DddR$^-$ mutant.

Although the *Marinomonas dddT*, *dddB*, and *dddC* genes were not required to confer a Ddd$^+$ phenotype to *E. coli*, their location suggested that they might be involved in DMSP catabolism. DddT may be required for DMSP uptake because it is in the betaine-carnitine-choline-

Table 1. Effects of cloned and mutant *ddd* genes and pregrowth in DMSP on DMS production. Wild-type and Ddd$^-$ mutant *Marinomonas* MWYL1, *B. cepacia* AMMD, *Rhizobium* NGR234, and *E. coli* containing various combinations of cloned *ddd* genes were examined. Strains were grown in appropriate minimal media with glycerol (G) or glycerol plus DMSP (G + D). DMS emissions are in nmol DMS min^{-1} mg dry weight^{-1}. Details of pBIO plasmids containing cloned *ddd* genes are in table S1. ND indicates not detectable; NT, not tested. Values for *Marinomonas* MWYL1 wild type grown in DMSP as sole C source averaged 12,095 ± 302 (± SE), indicating that the addition of a second, utilizable carbon source may slightly depress DMS emission.

Status of *ddd* gene	DMS emission after pregrowth in	
	G	G + D
	Marinomonas MWYL1	
Wild type	89 ± 27	7716 ±148
DddD$^-$ mutant	ND	ND
DddR$^-$ mutant	ND	ND
	E. coli	
None added	ND	ND
dddD-dddTBCR from MWYL1	150 ± 27	604 ± 45
	B. cepacia AMMD	
Wild type	120 ± 18	391 ± 34
	Rhizobium NGR234	
Wild type	170 ± 25	1432 ± 77
	E. coli	
dddD from *B. cepacia* AMMD	NT	236 ± 5
dddD from *Rhizobium* NGR234	NT	402 ± 54

Table 2. Effect of *dddR* of *Marinomonas* MWYL1 and *B. cepacia* AMMD on *ddd-lacZ* expression. Strains of *E. coli* and *Marinomonas* containing *dddD-lacZ* fusion plasmid pBIO1603 were grown as in Table 1. Derivatives of *E. coli* containing cloned *dddR* of *Marinomonas* MWYL1 (in pBIO1601) or *B. cepacia* AMMD (in pBIO1608) were assayed for β-galactosidase in triplicate.

Status of *dddR* gene	*dddD-lacZ* expression β-galactosidase activity (Miller units with SE)	
	G	G + D
	E. coli	
Absent	11 ± 4	9 ± 3
Cloned *dddR* of *Marinomonas* MWYL1	82 ± 9	1065 ± 124
Cloned *dddR* of *B. cepacia* AMMD	69 ± 14	1495 ± 30
	Marinomonas MWYL1	
Wild type	61 ± 12	4700 ± 176

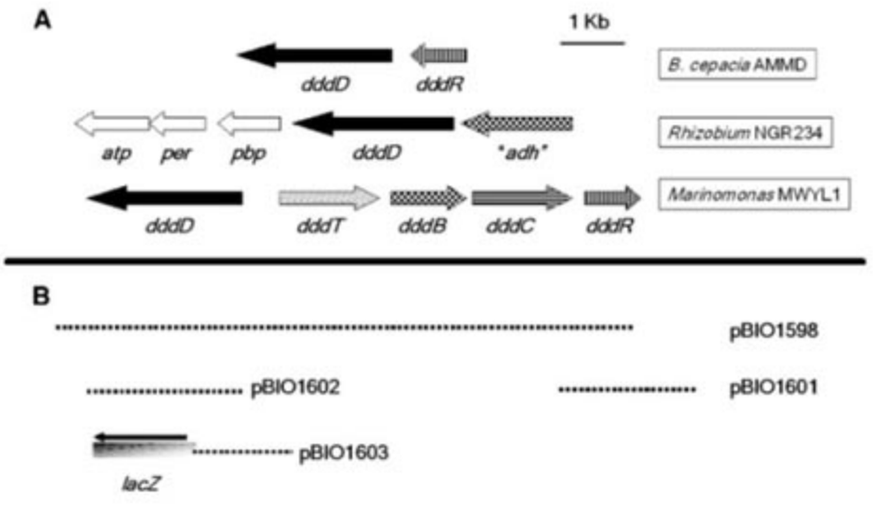

Fig. 2. The ddd regions of *Marinomonas* MWYL1, *B. cepacia* AMMD, and *Rhizobium* NGR234. (**A**) Genes are shown as arrows. The product of "*adh*" in NGR234 is related to alcohol dehydrogenase, as is DddB (hatched arrow). The *atp*, *per*, and *pbp* gene products are, respectively, the predicted adenosine triphosphatase (ATPase), permease, and periplasmic binding protein of an ATP-binding cassette (ABC) transporter of betaine-like molecules in *Rhizobium* NGR234. (**B**) Dimensions of cloned *Marinomonas ddd* genes in various plasmids (table S1). The dimension of the *dddD-lacZ* fusion pBIO1603 is also shown.

transporter (BCCT) family, whose members transport different betaine molecules. DddB is in the family of Fe-containing alcohol dehydrogenases, and DddC is a predicted methylmalonate-semialdehyde dehydrogenase-like protein. In *E. coli*, the transporters for betaine (BetU) and carnitine (CaiT) are, respectively, 45% and 27% identical to DddT and so may substitute for the bona fide DddT of *Marinomonas*.

The two Ddd$^+$ strains of *Rhizobium* and *Burkholderia* have unusually wide host ranges on angiosperms, so we speculate that their hosts may include species that, like *Spartina*, make DMSP. Neither *B. cepacia* nor *Rhizobium* NGR234 used DMSP as a sole carbon source under our conditions. However, their partial catabolism of DMSP, forming DMS, may have a role in detoxification or in signaling. Also unexpected is that the predicted function of DddD is a type III acyl CoA transferase, very different from the DMSP lyase that was hypothesized to cleave DMSP directly (*7*) (Fig. 1). Given its homology to *E. coli* CaiB, DddD is predicted to add CoA to DMSP, a key step preceding subsequent cleavage and release of DMS. The proposed DMSP-CoA thioester may be catabolized by one or more steps to DMS plus 3-hydroxypropionate (Fig. 1). This scheme could accommodate the observations (*20*) that a Ddd$^+$ α-proteobacterium, when grown on DMSP, produced DMS and accumulated 3-hydroxypropionate but not acrylate, a predicted product of DMSP lyase (Fig. 1).

CaiB of *E. coli* is a homodimer of two separate CaiB polypeptides (*21*). In contrast, the DddD proteins in the Ddd$^+$ bacteria shown in fig. S1 are all about twice the size of *E. coli* CaiB and comprise tandem, imperfect repeats separated by a poorly conserved linker (fig. S1). The homology between these DddD intramolecular repeats is greatest at their N-termini, which include the active site for CaiB (fig. S1). Therefore, a single DddD polypeptide may form the dimer-type structure for acyl CoA transferases whose substrate is DMSP.

The genes in the published Sargasso Sea bacterial metagenome (*22*) include one homolog each of DddD (58% identical) and DddR (60% identical). Therefore, the Ddd system occurs in oceanic bacteria, although less frequently than does the DmdA DMSP demethylase (*14*). Other bacteria may have different ways of making DMS from DMSP, because we noted that *dddD* homologs are absent from two other DMS-emitting strains, *Sulfitobacter* sp. EE-36 and *Roseovarius nubinhibens* ISM. It will be of interest to determine the range of different mechanisms for DMSP catabolism in bacteria and to understand their roles in global sulfur and carbon cycles.

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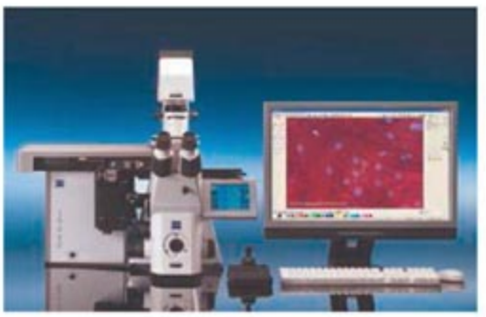
23. We thank T. Davy, M. Maidment, K. McGuire, and D. Cone for technical contributions; B. Broughton and E. Mahenthiralingam for providing strains; M. A. Moran for useful discussions; and the Joint Genome Initiative and the U.S. Department of Energy for sequencing. We also appreciate the editor's and anonymous reviewers' constructive comments. The project was funded by the Biotechnology and Biological Sciences Research Council and Natural Environment Research Council of the UK and the European Commission Framework. L.S. was supported by a Derek Bryan Scholarship of the University of East Anglia. Accession numbers are at National Center for Biotechnology Information as follows: *Marinomonas* MWYL1 DddD ZP_01598691, DddT ZP_01598692, DddB ZP_01598693, DddC ZP_01598694, and DddR ZP_01598695; *Marinomonas* MED121 DddD (ZP_01078425); marine gamma proteobacterium HTCC2207 DddD (ZP_01224900); *Rhizobium* NGR234 DddD (AAQ87407); *B. cepecia* AMMD DddD (YP_776185) and DddR (YP_776186); *S. pomeroyii* DSS-3 DddD (YP_166942); *S. stellata* E37 DddD (SSE37_17628); *E. coli* K12 CaiB (NP_414580); Sargasso Sea metagenome DddD (EAK74524) and DddR (EAI34472).

Supporting Online Material

www.sciencemag.org/cgi/content/full/315/5812/666/DC1
Materials and Methods
Fig. S1
Table S1
References and Notes

20 September 2006; accepted 21 December 2006
10.1126/science.1135370



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Tilton School	Tilton, NH	$775	$710	$615	$600	$535	$440
Tilton School	(GRS: Plant Metabolic Engineering)	$300	$285	$255	$300	$285	$255
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List of Session II meetings with confirmed sessions and speakers as of January 11, 2007
(discussion leaders are italicized):

ADVERSE DRUG REACTIONS
COLBY COLLEGE
WATERVILLE, ME
JUN 10-15, 2007
THOMAS KAWABATA, CHAIR
B KEVIN PARK, VICE CHAIR

- **Keynote Talk: The Future Safety of Clinical Trials of Innovative Medicines**
  (Gordon Duff)
- **Mitochondrial Toxicity**
  (*Yvonne Will*)
- **Novel Molecular Targets and Implications for Toxicity Testing**
  (*Mary Jane Masson*)
- **Adverse Drug Reactions with Biological Therapeutics: Mechanisms and Testing Approaches**
  (*Janet Clarke*)
- **Nanotechnology Applications in the Development of Therapeutics**
  (*Nakissa Sadrieh*)
- **Drug-Induced Liver Injury: Mechanisms that Involve the Innate and Adaptive Immune Responses**
  (*Neil Kaplowitz*)
- **Functional Genomic Approaches to Adverse Drug Reactions**
  (*James Stevens*)
- **Discussion Session: Adverse Drug Reactions - Which Ones Can We Predict?**

AGING, BIOLOGY OF
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 23-28, 2007
HOLLY BROWN-BORG,
ALEXANDER BUERKLE &
LA DORA THOMPSON, CO-CHAIRS
PAMELA LARSEN, JANET LORD &
DAVID SINCLAIR, CO-VICE CHAIRS

- **Keynote Lecture: Calorie Restriction and Life Span Extension - A Genetic Pathway in the Fly**
  (*Andrzej Bartke* / Steve Helfand)
- **Impact of DNA Damage and Repair Functions on Aging**
  (*Jan Vijg* / Jan Hoeijmakers / Frederick Alt / Maria Blasco / Tinna Stevnsner / Tomas Prolla)
- **Accelerated Aging**
  (*Vilhelm Bohr* / Makoto Kuro-o / Stephen Young / Tom Misteli)
- **Protein Folding / Aggregation / Degradation in Aging**
  (*Ana Maria Cuervo* / Thomas Nyström / Andrew Dillin / Rod Levine / Bertrand Friguet / Deborah Ferrington)
- **Immunoscenescence / Lipid Signaling and Aging**
  (*Rita Effros* / Graham Pawelec / Beatrix Grubeck-Loebenstein / Linda Partridge / Patrick Schrauwen)
- **Stem Cells**
  (*George Martin* / Dan Gottschling / Nadia Rosenthal / Piero Anversa / Charlotte Peterson / Jonathan Tilly)

Celebrating our 75th Anniversary on the Frontiers of Science (1931-2006)

- **The Role of Nuclear Receptors in Aging**
(*Gordon Lithgow* / Adam Antebi / Gretchen Darlington / J. Christopher Corton / David Moore)
- **Stress Resistance and Health Span**
(*Cynthia Kenyon* / Monica Driscoll / Tom Johnson / Arlan Richardson / Heinz Osiewacz)
- **Interventions and Healthy Aging**
(*Pamela Larsen* / *Janet Lord* / *David Sinclair* / Rafael de Cabo / Cathy Wolkow / Etienne Baulieu / Alberto Chiarugi)

AMYGDALA IN HEALTH & DISEASE
BATES COLLEGE
LEWISTON, ME
JUL 29-AUG 3, 2007
ANDREAS LUTHI & PANKAJ SAH, CO-CHAIRS
JOE LEDOUX & DENIS PARE, CO-VICE CHAIRS

- **The Amygdala and Emotional Memories**
(*Mort Mishkin* / Joseph LeDoux / Raymond Dolan)
- **Synaptic Plasticity**
(*Patricia Shinnick-Gallagher* / Denis Pare / Roberto Malinow / Vadim Y. Bolshakov / Po-Wu Gean)
- **Neuromodulation**
(*Donald Rainnie* / James L. McGaugh / Anthony A. Grace)
- **Fear Conditioning**
(*Asla Pitkanen* / Stephen Maren / Michael S. Fanselow / Hans Christian Pape / Jeansok J. Kim)
- **Extinction**
(*Michael Rogan* / Greg J. Quirk / Anthony A. Grace / Michael Davis)
- **Appetitive Conditioning/Addiction**
(*Alex J. McDonald* / Michela Gallagher / Barry J. Everitt / Richard F. Westbrook / Ronald E. See)
- **Physiological Function**
(*Patrik Vuilleumier* / Christian Buchel / Paul J. Whalen)
- **Psychological Disorders**
(*Ahmad Hariri* / Joy Hirsch / Douglas Bremner / Roger K. Pitman / Wayne C. Drevets)
- **Translational Research**
(*Bruce McEwen* / Sumantra Chattarji / Christian Grillon)

ANGIOGENESIS & MICROCIRCULATION
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 19-24, 2007
DOUGLAS HANAHAN, CHAIR
DONALD MCDONALD, VICE CHAIR

- **Keynote Talk 1: Roles of Cadherins and Catenins in Endothelial Cell-to-Cell Communication and the Regulation of Angiogenesis**
(Elisabetta Dejana)
- **Keynote Talk 2: Cellular Specialization in the Angiogenic Sprout: On the Roles of VEGF-, PDGF- and Notch Signaling**
(Christer Betsholtz)

ANTIGEN CROSS-PRESENTATION
BIG SKY RESORT
BIG SKY, MT
SEP 2-7, 2007
MATTHEW ALBERT &
PRAMOD SRIVASTAVA, CO-CHAIRS
SHANNON TURLEY, VICE CHAIR

- **Cell Death**
(Seamus Martin / Guido Kroemer / Ann Marshak-Rothstein)
- **Antigen Transfer to Dendritic Cells I**
(*Stephen Schoenberger* / Ton Schumacher / Margaret Callahan / Nir Hacohen / William Heath)
- **Antigen Transfer to Dendritic Cells II**
(*Peter Cresswell* / Robert Binder / Michel Desjardins)
- **Endogenous Alarm Signals**
(*Michael Lotze* / Kevin Tracey / Caetano Reis e Sousa / Kenneth Rock)
- **Antigen Capture**
(*Lynda Stuart* / Patrick Williamson / Nathalie Franc / Lucas Pelkmans)
- **Phagosome Maturation**
(*Sergio Grinstein* / Colin Watts / Sebastian Amigorena / Ira Mellman)
- **Antigen Processing & Presentation**
(*Shannon Turley* / Nilabh Shastri / Jonathan Yewdell / Wilfred Jefferies)
- **Clinical Interface**
(*Hyam Levitsky* / Herbert "Skip" Virgin / Warren Shlomchik)
- **Historical Perspective / Evolution**
(*Charles David* / Jean-Claude Ameisen / Michael Bevan)

APOPTOTIC CELL RECOGNITION & CLEARANCE
BATES COLLEGE
LEWISTON, ME
JUN 17-22, 2007
KODI RAVICHANDRAN &
MICHAEL HENGARTNER, CO-CHAIRS
MARTIN HERRMANN &
YOSHINOBU NAKANISHI, CO-VICE CHAIRS

- **Keynote Talk 1: Playing Hide & Seek with Phosphatidylserine**
(Robert Schlegel)
- **Keynote Talk 2: Systems Analysis of Phagocytosis**
(Lynda Stuart)
- **Getting together: Phagocytic Receptors and Ligands I**
(*Yoshi Nakanishi* / Shyra Gardai / Giovanna Chimini / Zheng Zhou)
- **Phagocytic Receptors and Ligands II**
(*Robert Schlegel* / Peter Henson / Nathalie Franc)
- **Good Eating Habits: Mechanisms of Ingesting and Digesting Corpses**
(*Kodi Ravichandran* / Ray Birge / Shige Nagata / Lars-Peter-Erwig)
- **Nibbling on the Food: Pruning of Axons and Damaged Neurons by Glial Cells**
(*Michael Hengartner* / Marc Freeman / Yoshi Nakanishi)
- **After the Meal Issues: Consequences of Engulfment**
(*Peter Henson* / Scott Kiss / Adam Lacy-Hulbert / Laszlo Fesus)
- **Leaving Food Behind: Immunogenicity of Unengulfed Corpses**
(*Chris Gregory* / Martin Herrmann / Pramod Srivatsava)
- **Test Tube to Therapy: Clinical Uses of Apoptotic Cells**
(*Dave Peritt* / James George / Adrian Morrelli / James Ferrara / Terry Fry)
- **Desserts: New Developments**
(*Martin Herrmann* / Chris Gregory)

APPLIED & ENVIRONMENTAL MICROBIOLOGY
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 15-20, 2007
KENNETH NEALSON, CHAIR
NICOLE DUBILIER, VICE CHAIR

- **New Metabolic Pathways**
- **Electricity and Hydrogen from Microbes**
- **Microbes as Environmental Biosensors**
- **Mechanisms of Extracellular Electron Transfer**
- **Biofilm Formation and Stability**
- **New Technology for Imaging Microbes**
- **New Technology for Measuring Microbial Processes**
- **Microbial Diversity, Genomics, and Metagenomics**

ARCHAEA: ECOLOGY, METABOLISM & MOLECULAR BIOLOGY
PROCTOR ACADEMY
ANDOVER, NH
AUG 19-24, 2007
IMKE SCHROEDER &
MALCOLM WHITE, CO-CHAIRS
JULIE MAUPIN-FURLOW &
BETTINA SIEBERS, CO-VICE CHAIRS

- **Keynote Talk: Starting and Stopping Transcription**
(*Imke Schröder* / John Reeve)
- **Recombination and Repair**
(Thorsten Allers / Ed Bolt / Isaac Cann / Jocelyne DiRuggiero / Denis Grogan)
- **Gene Regulation**
(Haruyuki Atomi / Paul Blum / Robert Gunsalus / William Metcalf / John van der Oost / Ruth Schmitz)
- **Information Processing: From DNA to Protein**
(Steve Bell / Joseph Krzycki / Dieter Söll)
- **Protein Translocation and Processing**
(Sonja Albers / Jerry Eichler / Peter Lund / Julie Maupin-Furlow)
- **Evolution and the Tree of Life**
(Patrick Forterre / Eugene Koonin)
- **Ecology of Emerging Archaea**
(*Karl Stetter* / Edward Delong / Jim Elkins / Christa Schleper / Dave Stahl)
- **Evolution and Composition of Microbial Communities**
(Antje Boetius / Edward DeLong)
- **Archaeal Proteins and Physiology**
(Arnulf Kletzin / Biswarup Mukhopadhyay / Rolf Thauer / Simon de Vries / Robert White)
- **Physiology and Regulation of Carbohydrate Metabolism**
(*William Whitman* / Peter Schönheit / Bettina Siebers)

ASSISTED CIRCULATION
BIG SKY RESORT
BIG SKY, MT
AUG 19-24, 2007
LESLIE MILLER, CHAIR
JOHN WATSON, VICE CHAIR

- **Where are we now? INTERMACS Update**
  (*Jim Kirklin* / *Jim Young*)
- **Where are we now? Industry Update**
  (*Mike Acker* / *George Weiselthaler* /
  Jim Long / George Noon)
- **Putting an End to Complications of MCS: Innovative Ideas and Best Practices**
  (*Mariell Jessup* / *Randy Starling* /
  Keith Aaronson / William Harmon / Don Hill)
- **Biologic Responses of MCS (Including Anti- Aggregation/Coagulation)**
  (*Gary Eikelboom* / Guillermo Torre /
  Ed Titel / Silviu Itescu / Dan Birkoff)
- **Designing the Next Clinical Trials**
  (*Eric Rose* / *Les Miller* /
  Lynn Warner Stevenson / Marv Konstam /
  Annetine Gelijns / David Farrar)
- **Regulatory/Funding/Industry Constraints in Clinical Trials**
  (*Bob Kormos* / Jeff Nelson /
  Bram Zuckerman / Don Middlebrook /
  Jane Reedy)
- **Innovations in Technology to Advance the Field and Enhance QOL for Patients**
  (*John Watson* / *Tim Baldwin* / Jim Anderson /
  Harvey Borovitz / Steven Boyce / Jeff Rose)
- **True LV Recovery: How Do We Quadruple the Percent of Patients Weaned Off Devices?**
  (*Magdi Yacoub* / *Frank Pagani* /
  Doris Taylor / Ken Chien / Jennifer Hall /
  Emma Birks Harefield)
- **Goals for MCS in 2012**
  (*Les Miller* / *John Watson*)

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LUCCA (BARGA), ITALY
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CHRISTOPHER GLASS &
MICHAEL ROSENFELD, CO-CHAIRS
MARTHA CATHCART, VICE CHAIR

- **Nuclear Receptors and Coregulators**
  (*Johan Auwerx* / Peter Tontonoz /
  Jorge Plutzky)
- **Innate and Acquired Immune Mechanisms**
  (*Goran Hansson* / Joseph Witzum /
  Ziad Mallat / Linda Curtiss)
- **Genetics**
  (*Helen Hobbs* / Jake Lusis / Steve Young)
- **Advanced Plaque: Death, Disruption, Thrombosis and Calcification**
  (*Ira Tabas* / Alain Tedgui / Peter Libby /
  Linda Demer)
- **Imaging**
  (*Chun Yuan* / Zahi Fayad / Johannes Schaar)
- **Macrophage Biology and Inflammation**
  (*Alan Aderem* / Siamon Gordon /
  Isreal Charo / Kathryn Moore)
- **Vascular Cell Sources and Phenotypes**
  (*Seppo Yla-Hertulla* / Gwendalyn Randolph /
  Stefanie Dimmeler)
- **Lipid Metabolism and Reverse Cholesterol Transport**
  (*Alan Tall* / Carl Sparrow / Rudolph Zechner /
  Bob Farese)
- **Diabetes and Metabolic Syndrome**
  (*Bart Staels* / Takashi Kadowaki / Alan Attie)

ATMOSPHERIC CHEMISTRY
BIG SKY RESORT
BIG SKY, MT
AUG 26-31, 2007
DOUGLAS WORSNOP, CHAIR
PAUL WENNBERG, VICE CHAIR

- **Key Perspectives**
  (*Barbara Finlayson-Pitts* / Guy Brasseur /
  Andi Andreae)
- **Field Observations**
  (*Sasha Madronich* / Dwayne Heard /
  Steve Brown / Scott Herndon / Min Shao)
- **Aerosol Chemistry**
  (*John Seinfeld* / Urs Baltensperger /
  Allen Goldstein / Hugh Coe)
- **Lab Kinetics**
  (*Kristie Boering* / Paul Wine /
  Jonathan Abbatt)
- **Models, Clouds, Nucleation**
  (*Dan Murphy* / Ken Carslaw /
  Thanos Nenes / Markku Kulmala)
- **CO_2 Budgets**
  (*Ralph Keeling* / Steve Wofsy / David Archer)
- **Global Perspectives**
  (*Jennifer Logan* / Alex Guenther /
  Lyatt Jaegle / Steve Ghan)
- **Upper Atmosphere**
  (*Dave Fahey* / Thomas Roeckmann /
  Nathaniel Livesey / Brian Toon)

ATOMIC PHYSICS
TILTON SCHOOL
TILTON, NH
JUL 1-6, 2007
CHRIS MONROE, CHAIR
PROTIK MAJUMDER, VICE CHAIR

- **Quantum Information**
  (*Carl Williams* / David Wineland /
  Gavin Brennan)
- **Degenerate Gases I**
  (*Keith Burnett* / Zoran Hadzibabic)
- **Degenerate Gases II**
  (*Dan Stamper-Kurn* / Randy Hulet)
- **Condensed Matter Links**
  (*Jason Ho* / Keith Schwab /
  Richard Scalettar)
- **Precision Measurements**
  (*Dan Kleppner* / Gerald Gabrielse /
  Wim Ubachs / Till Rosenband)
- **Atomic Interactions**
  (Brett Esry / Georg Raithel)
- **Attosecond Physics**
  (*Phil Bucksbaum* / Paul Corkum /
  Mark Kasevich)
- **Quantum Optics**
  (*Vlad Vuletic* / Jeff Kimble / Mark Raizen)
- **Bio-Molecular Imaging**
  (*Jennifer Ogilvie* / Warren Warren /
  Yaron Silberberg)

BARRIER FUNCTION OF MAMMALIAN SKIN
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 5-10, 2007
ANTHONY RAWLINGS &
MIKE ROBERTS, CO-CHAIRS
WALTER HOLLERAN &
NEIL KITSON, CO-VICE CHAIRS

- **Keynote Talk: How Barrier Dysfunction Trumps Immunological Abnormalities in Atopic Dermatitis**
  (*Steven Hoath* / Peter Elias)
- **The Adaptive and Reactive Barrier**
  (*Neil Kitson* / Daniel Maes /
  David Basketter / Michael Cork)
- **Stratum Corneum Formation and Maturation**
  (*Tony Rawlings* /
  Eleftherios Diamandis / Michel Simon /
  Erwin Tschachler / Irwin McClean)
- **Emerging Epidermal Barrier Functions**
  (*Walt Holleran* / Ken Feingold /
  Faith Williams / Richard Gallo / Des Tobin)
- **Skin Biomechanics**
  (*Howard Maibach* / Birgit Lane /
  Reiner Dauskardt / Mark Kendall)
- **Strategies to Maximize and Assess Skin Penetration**
  (*Mike Roberts* / Annette Bunge /
  Richard Guy / Russ Potts)
- **Consequences of Affecting or Crossing the Skin Barrier**
  (*Bill Dressler* / Chris Anderson /
  Nancy Monteiro-Riviere /
  Gerhard Nohynek / Bob Bronaugh)
- **Hot Topics & Selections from Poster Contributions**
  (*Jerry Kasting* / Julia Caussin /
  Florence Puch / Jim Riviere / Sheree Cross /
  Audra Stinchcomb / poster contributions)
- **Lifestyle and Barrier Function**
  (*Raman Govindarajan* / Jens Thiele /
  Johan Wiechers / Miri Seiberg /
  Juergen Lademann)
- **A Debate on: Do Corneocytes Leak?**
  (*Peter Elias* / Ken Walters / Joke Bouwstra)

BIOINFORMATICS: THE INTERFACE OF COMPUTATION AND EXPERIMENT
PROCTOR ACADEMY
ANDOVER, NH
JUL 15-20, 2007
EDWARD MARCOTTE, CHAIR
CHRIS BURGE, VICE CHAIR

- **Keynote Lectures: Quantitative Biotechnology**
- **Randomness and Noise in Biological Systems**
  (Rachel Brem / Erin O'Shea /
  Alexander van Oudenaarden)
- **Synthetic Biology**
  (*Adam Arkin*)
- **Comparative Genomics**
  (*Fritz Roth* / Gil Bejerano / Bruce Taillon)
- **Gene Regulatory Codes: Chromatin, Transcriptional and Posttranscriptional Codes**
  (Martha Bulyk / Chris Burge /
  Anton Enright / Zhiping Weng)
- **Computational Systems Biology and Proteomics**
  (Amy Keating / Robert Murphy /
  Dana Pe'er / Robert Waterston)
- **Structure, Evolution, and Dynamics of Biological Networks**
  (Michael Laub / Hanah Margalit / Aviv Regev)
- **Genome Evolution**
  (*William Press* / Hunter Fraser /
  Eugene Koonin / Svante Pääbo)
- **Genomic Medicine**
  (Bertie Göttgens / Eric Schadt)

BIOLOGICAL MOLECULES IN THE GAS PHASE
BATES COLLEGE
LEWISTON, ME
JUL 22-27, 2007
ALBERT HECK, CHAIR
DAVID PRATT &
JOAN-EMMA SHEA, CO-VICE CHAIRS

- **Keynote Talk: Serine - Chemistry, Clusters and the Origin of Life**
  (Graham Cooks)
- **Hydrated Biomolecules in the Gas-Phase**
  (*Evan Williams* / David Pratt / Vitaly Kresin / Rebecca Jockusch)
- **Macromolecular Mass Spectrometry**
  (*Julie Leary* / Robert van den Heuvel / Lars Konermann / John Klassen)
- **Protein Folding and Conformation by H/D Exchange Mass Spectrometry**
  (*John Engen* / Elizabeth Komives / Igor Kaltashov / Thomas Jorgensen)
- **High-Resolution Spectroscopy of Peptides, Experimental Results**
  (Leo Meerts / Lavina Snoek / Mattanjah de Vries / Nick Polfer)
- **Related Condensed Phase Approaches**
  (Tobias Baumgart / Philip Anfinrud / Haw Yang)
- **Oxidation, Electron Transfer & Other Chemical Probes for Protein Conformation**
  (*Vicky Wysocki* / Roman Zubarev / Kathrin Breuker / Michael Gross)
- **Computational Approaches to Protein Conformation**
  (*Joan-Emma Shea* / John E. Straub / Leonid Mirny / Sean Decatur)
- **High-Resolution Spectroscopy of Peptides, Theory and Experiment**
  (Benny Gerber / Jerzy Leszczynski)

BIOMATERIALS:
BIOCOMPATIBILITY / TISSUE ENGINEERING
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 22-27, 2007
ANDRES GARCIA, CHAIR
WILLIAM REICHERT, VICE CHAIR

- **Keynote 1: Creation of Functional Vessels for Cancer Therapy and Tissue Engineering**
  (Rakesh Jain)
- **Keynote 2: Cell Signaling Networks**
  (Douglas Lauffenburger)
- **Device Biological Performance**
  (*Patrick Stayton* / William Shain / Thomas Bauer / Howard Griesler)
- **Modeling Protein Adsorption**
  (*David Grainger* / Igal Szleifer / Robert Latour)
- **Directed Tissue Repair**
  (*Kevin Healy* / Ravi Bellamkonda / Dan Gazit / François Auger)
- **Tissue Responses to Physical Stimuli**
  (*Joyce Wong*/ Sangeeta Bhatia / David Kaplan)
- **Delivery of Therapeutics**
  (*Shelly Sakiyama-Elbert* / Ravi Kane / Lonnie Shea / Kristi Kiick)
- **Advances in Biomaterials Engineering**
  (*Jeff Hubbell* / Jennifer Elisseeff / Darrell Irvine)
- **Engineering Host Responses**
  (*Julia Babensee* / Themis Kyriakides / Jeff Davidson / Ron Gill)
- **Keynote 3: Physics and Technology Discharged from Franklin's Kite Experiment**
  (*Monty Reichert* / Robert McGrath)

BIOORGANIC CHEMISTRY
PROCTOR ACADEMY
ANDOVER, NH
JUN 10-15, 2007
JESSICA FRIEDMAN &
BLAKE PETERSON, CO-CHAIRS
PAUL RICHARDSON &
WILFRED VAN DER DONK, CO-VICE CHAIRS

- **Single Molecules and Biophysical Methods**
  (*Claudio Chuaqui* / Maria Pellegrini / Robert Singer / Sunney Xie)
- **Model Systems**
  (*Sergey Savinov* / Matthew Francis / Indraneel Ghosh / Jacqueline Barton / William DeGrado)
- **Frontiers in Enzymology**
  (*Lizbeth Hedstrom* / Robert Copeland / Donald Hilvert / Stephen Benkovic)
- **Drug Design and Discovery**
  (*John Starrett* / Jay Grobler / Stewart Fisher / Andrea Cochran / Timothy Willson)
- **Transcription Factors and DNA Repair**
  (*Orlando Schaerer* / John Koh / John Essigmann / Gregory Verdine)
- **Visualizing Cellular Biology**
  (*James Chen* / Jennifer Lippincott-Schwartz / Kai Johnsson / Peter Sorger / Tom Kirchhausen)
- **Molecular and Cellular Probes**
  (*Jeffrey Bode* / Gregor Zlokarnik / Paul Hergenrother / Milan Mrksich)
- **Emerging Areas in Chemical Biology**
  (*Jason Gestwicki* / Helen Blackwell / Nicole Sampson / James Wells / Gerald Crabtree)
- **New Paradigms in Bioorganic and Medicinal Chemistry**
  (*Brian Blagg* / Dale Boger / Andrew Hamilton / Francois Diederich)

BONES & TEETH
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 15-20, 2007
PAMELA ROBEY, CHAIR
BRENDAN BOYCE, VICE CHAIR

- **Epigenetic Control in Skeletal Biology and Pathology**
  (*Gary Stein* / Anthony Imbalzano / James Davie)
- **Skeletal Development**
  (*Bjorn Olsen* / Stefan Mundlos / Yingzi Yang / Rudolf Grosschedl / Gerard Karsenty)
- **The Cell and Molecular Biology of Oral Tissues**
  (*Martha Somerman* / Carolyn Gibson / Paul Sharpe / Malcolm Snead)
- **Bone and Hematopoiesis**
  (*Paolo Bianco* / Ana Cumano / David Scadden / Toshio Suda)
- **Osteoimmunology**
  (*Brendan Boyce* / Roberto Pacifici / Mary Beth Humphrey)
- **Bone Metastases: Insight into Mechanisms and Novel Treatments**
  (*Theresa Guise* / Olivier Peyruchaud / Yibin Kang / Kenneth Pienta)
- **FGF-23 in Calcium and Phosphate Metabolism**
  (*Gordon Strewler* / Itaru Urakawa / Beate Lanske)
- **The Biological Basis of Bone Therapies**
  (*Serge Ferrari* / Jack Martin / Fraser Coxon / Paul Kostenuik)
- **Special Lecture: Bioarcheology and Hidden Truths of the Skeleton**
  (Jane Buikstra)

CALCIUM SIGNALLING
TILTON SCHOOL
TILTON, NH
JUL 8-13, 2007
INDU AMBUDKAR, CHAIR
ALEXEI TEPIKIN, VICE CHAIR

- **Membrane Domains in Signaling**
  (*Jim Putney* / Annette Dolphin / Barbara Baird)
- **Sensory and Transduction Mechanisms**
  (*Donald Gill* / Baruch Minke / Wolfgang Liedtke / Tamas Balla / Atsushi Miyawaki)
- **Ca^{2+} Stores and Ca^{2+} Release Mechanisms**
  (*Kevin Foskett* / David Yule / Susan Hamilton / Eduardo Rios)
- **Mechanisms of Ca^{2+} Entry**
  (*Colin Taylor* / Tobias Meyer / Anjana Rao / Bernd Nilius)
- **Organization of Channel-Signalling Complexes**
  (*Ole Petersen* / Katsuhiko Mikoshoba / Richard Huganir / Clara Franzini-Armstrong)
- **Mitochondrial Ca^{2+}: Bioenergetics and More**
  (*Alexei Tepikin* / Tulio Pozzan / Guy Rutter / Wolfgang Graier)
- **Interaction of Ca^{2+} with Other Signalling Mechanism**
  (*Shmuel Muallem* / Alderbaran H / Shamshad Cockcroft / John Scott)
- **Ca^{2+} in Physiology and Disease**
  (*Ernesto Carafoli* / Gary Shull / Rene Bindels / Daniella Pietrobon / Pierluigi Nicotera)
- **Keynote Lecture: TRP Channels: Roles in Sensory Signal and Human Health and Disease**
  (*Indu Ambudkar* / Craig Montell)

CANCER MODELS & MECHANISMS
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
AUG 26-31, 2007
WILLIAM KAELIN, CHAIR
GERARD EVAN, VICE CHAIR

- **Keynote 1: Cancer Systems Biology**
  (Marc Vidal)
- **Keynote 2: Advances in Molecular Imaging**
  (Chris Contag)
- **Flies and Worms I**
  (Tian Xu / Norbert Perrimon)
- **Flies and Worms II**
  (Gary Ruvkun / Jo Anne Powell Coffman)
- **Frogs and Fish I**
  (Stephano Piccolo / Jackie Lees)
- **Frogs and Fish II**
  (Keith Cheng / Edwin Cuppen)
- **Mice and Men I**
  (Erwin Wagner / Andreas Trumpp)
- **Mice and Men II**
  (Gerard Evan / Ned Sharpless)
- **Mice and Men III**
  (Rene Bernards / Wilhelm Krek)
- **Chemistry and Nanotechnology**
  (Steven Quake / Tarun Kapoor)

CANNABINOID FUNCTION IN THE CNS
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 30-OCT 5, 2007
MANUEL GUZMAN, OLIVIER MANZONI &
GIOVANNI MARSICANO, CO-CHAIRS
DANIELE PIOMELLI, VICE CHAIR

- **Opening Lecture: Cannabinoids - Quo Vadimus**
  (Raphael Mechoulam)
- **Endocannabinoid Signaling in the CNS**
  (*Ken Mackie* / Vincenzo Di Marzo / Ben Cravatt / Daniele Piomelli)
- **Endocannabinoids and Neuronal Circuitry: Pain**
  (*Andrea Hohmann* / T. Philip Malan Jr. / MacDonald J. Christie)
- **Endocannabinoids and Neuronal Circuitry: Learning and Plasticity**
  (*Pablo E. Castillo* / David Robbe / Carsten Wotjak)
- **Endocannabinoids and Neuronal Circuitry: Reward**
  (*Rafael Maldonado* / Taco J. de Vries / Emmanuel Valjent)
- **Endocannabinoids: Neuroinflammation and Signaling in Glial Cells**
  (*Nephi Stella* / David Baker / Carmen Guaza)
- **Endocannabinoids and Neural Development**
  (*David A. Greenberg* / Tibor Harkany / Ismael Galve-Roperh)
- **New Tools in Cannabinoid Research**
  (*Beat Lutz* / Mauro Maccarrone / Joseph P.Y. Kao)
- **Endocannabinoids in Central and Peripheral Metabolic Regulation**
  (*Gerard Le Fur* / George Kunos / Uberto Pagotto)
- **Closing Lecture: An Integrated Prospective on Cannabinoids Research**
  (George F. Koob)

CARBOHYDRATES
TILTON SCHOOL
TILTON, NH
JUN 17-22, 2007
TODD LOWARY & PENG WANG, CO-CHAIRS
PETER SEEBERGER &
STEPHEN WITHERS, CO-VICE CHAIRS

- **Glycoengineering**
  (*Steven Withers* / Xi Chen / Tillman Gerngross / Suzanne Walker)
- **Carbohydrate Processing Enzymes I**
  (*Todd Lowary* / Gideon Davies / Paul DeAngelis / David Vocadlo / Warren Wakarchuk)
- **Carbohydrate Processing Enzymes II**
  (*Nicola Pohl* / James Naismith / Martin Tanner / Lai-Xi Wang)
- **Glycopharmaceuticals I**
  (*Peng George Wang* / Linda Hsieh-Wilson / Chi-Huey Wong / Biao Yu)
- **Glycopharmaceuticals II**
  (*Peter Seeberger* / Chitrananda Abeygunawardana / Geert-Jan Boons / Sun-Ichiro Nishimura)
- **Structure and Bioinformatics**
  (*Mary Cloninger* / Julie Leary / Kay-Hooi Khoo / Christine Szymanski / Claus-Wilhelm von der Lieth)
- **Conformational Analysis and NMR Spectroscopy**
  (*Allen Bush* / Andrew Almond / Thomas Peters / Robert Woods)
- **Carbohydrate Synthesis I**
  (*Bertram Fraser-Reid* / David Crich / Robert Field / Shang-Chen Hung / Yasuhiro Kajihara)
- **Carbohydrate Synthesis II**
  (*Jacquelyn Gervay-Hague* / France-Isabelle Auzanneau / Mikael Bols / Makoto Kiso)

CATCHMENT SCIENCE: INTERACTIONS OF HYDROLOGY, BIOLOGY & GEOCHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 8-13, 2007
ELIZABETH BOYER &
HELEEN DE WIT, CO-CHAIRS
KEITH ESHLEMAN, VICE CHAIR

- **Back to Basics: New Insights into Biogeochemical Cycles**
  (*Bridget Emmett* / *Nancy Grimm* / Osvaldo Sala / Joshua Schimel / Whendee Silver / Ed Tipping)
- **Learning from Ecosystem Experiments**
  (*Jan Mulder* / *Lindsay Rustad* / Rick Hooper)
- **Toward Prediction of Coupled Cycles in Catchments**
  (*Larry Band* / *Penny Johnes* / Jack Cosby / Christina Tague / Andrew Wade)
- **Exploring Hypotheses About DOC Trends in Freshwaters**
  (*George Aiken* / *Chris Evans* / Chris Freeman / John Stoddard)
- **Catchment Science Poster Presentations**
  (Meeting participants)

CATECHOLAMINES
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
AUG 5-10, 2007
JILL BECKER, CHAIR
PATRICIO O'DONNELL, VICE CHAIR

- **Keynote Talk 1: Imaging the Addicted Brain**
  (*Terry E. Robinson* / Nora Volkow)
- **Keynote Talk 2: Dopamine Cell Transplantation in Parkinson's Disease**
  (*Marie-François Chesselet* / Anders Björklund)
- **Amino Acid - Dopamine Interactions**
  (*Paul Bolam* / Christian Luscher / Peter Kalivas / Mark Wightman)
- **Catecholamine and Neuroendocrinology**
  (*Paul Micevych* / Anne Etgen / Shaila Mani / Elaine Hull / Zuoxin Wang)
- **Catecholamine Release and Transporter Function**
  (*Ben Westerink* / David Sulzer / Randy Blakely)
- **Catecholamines and Neuronal Function: Lessons from Primates**
  (*Suzanne Haber* / Hagel Bergmann / Paul Apicella / Charles Bradberry)
- **Catecholamine Systems and Cognition**
  (Gary Aston-Jones / Craig Berridge)
- **Development, Differentiation, and Survival of Catecholamine Neurons**
  (*Gert ter Horst* / Lawrence Wilkinson / Christel Westenbroek / David Standaert)
- **Hot Topics**
  (*Regina Carelli*)

GRADUATE RESEARCH SEMINAR: CATECHOLAMINES
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
AUG 3-5, 2007
JILL BECKER, JONATHAN DILGEN,
CHERYSE FURMAN, SHANNON HARDIE &
KYLE SMITH, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Catecholamines** is a three-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Catecholamines** Gordon Research Conference will take place at the same location, immediately following the Seminar.

- **Catecholamine Regulation of Behavior, Cognition, and Neuroendocrine Function**
  (*Regina Carelli*)
- **Involvement of Catecholamines in Neurological and Neuropsychiatric Disorders**
  (*Nancy Bonini*)
- **Molecular Mechanisms of Catecholamine Signaling**
  (*David Sulzer*)

CELL BIOLOGY OF METALS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 29-AUG 3, 2007
ANDREW DANCIS &
JONATHAN GITLIN, CO-CHAIRS
VALERIA CULOTTA &
WALTER SCHAFFNER, CO-VICE CHAIRS

- **Metals into Cells**
  (*Andy Dancis* / Mary Lou Guerinot / Dennis Thiele)
- **Metals in Endocytic and Internal Compartments**
  (*Simon Labbe* / Caroline Enns / Mark Fleming / Sharon LaFontaine / Betty Eipper)
- **Mitochondria and Copper**
  (*Caryn Outten* / Dennis Winge / Eric Shoubridge / Val Culotta)
- **Mitochondria and Iron**
  (*Donna Gordon* / Barry Paw / Timothy Stemmler / Sonia Levi / Susan Hayflick)
- **Metals in Chloroplasts and Plants**
  (*Simon Knight* / Kenneth Cline / Marinus Pilon / Sabeeha Merchant)
- **Sensing of Metals in Organisms**
  (*Amanda Bird* / Nancy Andrews / Tracey Rouault / Jerry Kaplan / Walter Schaffner)
- **Nutrients, Metals, and Oxygen**
  (*Nigel Robinson* / Richard Bruick / Celeste Simon)
- **Metal Cofactors**
  (*Paula Fraenkel* / Roland Lill / Ralph Mendel / Michael Green / Iqbal Hamza)
- **Metal Allocation and Sensing**
  (*Jonathan Gitlin* / Thomas OHalloran / Anne-Laure Bulteau / Dave Eide)
- **Hot Topics and Poster Presentations**
  (*Mick Petris* / *Kerry Kornfeld*)
- **Alexander M. Cruickshank Lecture: Cellular Nutrient Homeostasis**
  (Erin O'Shea)

CELL GROWTH & PROLIFERATION
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 24-29, 2007
MICHAEL YAFFE, CHAIR
SALLY KORNBLUTH, VICE CHAIR

- **Keynote Talk 1: A Metabolic Switch for Converting Cell Growth into Proliferation** (Craig Thompson)
- **Keynote Talk 2: MitoCheck - A Combined Genomics / Proteomics and Chemical Biology Approach to Study Mitosis in Mammalian Cells** (Jan-Michael Peters)
- **Cell Cycle** (Wade Harper / Michele Pagano / Angelika Amon / Michael Tyers / James Ferrell)
- **Growth and G1 Control** (John Blenis / David Sabatini / Bob Duronio / Danny Lew)
- **Chromosome Replication and Dynamics** (Julian Blow / Anindya Dutta / Lea Harrington / Vicki Lundblad / Johannes Walter)
- **Mitosis** (Jon Pines / Bernard Ducommun / Michael Glotzer / David Pellman)
- **DNA Damage and Cell Cycle Checkpoints** (Steve Elledge / Karlene Cimprich / Rene Medema / Bill Dunphy / Jiri Bartek)
- **Oncogenes and Tumor Suppressor Genes** (Laura Attardi / Alea Mills / Eileen White / Scott Lowe)
- **Signal Transduction / Stem Cells** (Jean Wang / Sally Kornbluth / Karen Cichowski / Carla Bender-Kim / Angel Nebreda)
- **Cancer and Cancer Models / Clinical Applications** (Bill Hahn / M. Celeste Simon / Peter Friedl / Peter Jackson)

CELL-CELL FUSION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 1-6, 2007
AGNÈS VIGNERY & DIANA MYLES, CO-CHAIRS
WILLIAM MOHLER, VICE CHAIR

- **Keynote Talk: Membrane Fusion** (James Rothman)
- **Viral Fusion** (*Leonid V. Chernomordik* / Margaret Kielian / Yves Gaudin)
- **Sperm-Oocyte Fusion** (*Diana Myles* / Masaru Okabe)
- **Myoblast Fusion** (*Susan Abmayr* / Elizabeth Chen / Anton Bennett / Mary K Baylies)
- **Fusion in *C. elegans*** (*William Mohler* / Benjamin Podbilewicz)
- **Yeast Mating** (*Jodi Nunnari* / Eric Grote)
- **Cell Fusion in *Neurospora crassa* and in *Chlamydomonas*** (*Louise Glass* / William J. Snell)
- **Macrophage Fusion** (*Agnès Vignery* / Toshio Suda / Themis Kyriakides)
- **Life and Death: Stem Cell and Metastasis** (*Yuri Lazebnik* / Dominik Duelli)

CELLULAR OSMOREGULATION: SENSORS, TRANSDUCERS & REGULATORS
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
JUN 3-8, 2007
RAINER HEDRICH & PAUL YANCEY, CO-CHAIRS
VALERIE DAGGETT, VICE CHAIR

- **Keynote Talk1: Physiology and Pathophysiology of CLC Anion Channels and Transporters** (Thomas Jentsch)
- **Keynote Talk2: Turgor and Stress Relaxation in Growing Plant Cells - Dynamics and Molecular Underpinnings** (Daniel Cosgrove)
- **Osmosensing and Regulation in Microbes** (*Colin Hill* / Karlheinz Altendorf / Boris Martinac / Susanne Morbach / Bert Poolman / Bodil Nordlander)
- **Animal Volume Regulation – Transporters** (*Morris Baslow* / Jay M. Baltz / Stine F. Petersen / Eric Delpire)
- **Animal Volume Regulation – Disease** (*Clive Baumgarten* / Jennifer Bedford / Martha E. O'Donnell / Yasunobu Okada / Philippe Gual)
- **Animal Volume Regulation - Signal Transduction** (*Florian Lang* / Wolfgang Liedtke / Else K. Hoffmann / Freimut Schliess)
- **Macromolecule-Solute-Water Interactions** (*Zoya Igantova* / George Rose / Montgomery Pettitt / David S. Cafiso / Natalia A. Chebotareva)
- **Osmoregulation in Algae - Genes, Solutes and Transporters** (*Rainer Hedrich* / Colin Brownlee / Andreas Weber / Ulrich Zimmermann)
- **Osmoregulation in Higher Plants - Genes, Solutes and Transporters** (*Nava Moran* / Jose Pardo / Wei-Hua Wu / Norbert Sauer / Rob Roelfsema / Jose A. Feijo)
- **Osmoregulation in Higher Plants - Impact of Vacuolar Transport** (*Petra Dietrich* / Enrico Martinoia / Menachem Moshelian / Helene Barbier-Brygoo)

CELLULASES & CELLULOSOMES
PROCTOR ACADEMY
ANDOVER, NH
JUL 29-AUG 3, 2007
MARK MORRISON, CHAIR
HARRY GILBERT, VICE CHAIR

- **Setting the Stage: Matching Enzyme and Substrate** (*Doug Eveleigh* / Tuula Teeri / Ed Bayer)
- **Cell Wall Architecture and Display** (*Mike Himmel* / Shi-You Ding / Harry Brumer / Arthur Ragauskas / Junji Sugiyama)
- **Glycoside Hydrolase Structure and Function - Cellulosomal Module Interactions** (*Jean-Pierre Belaich* / Veronique Receveur-Brechot / Carlos Fontes / Steve Smith)
- **Glycoside Hydrolase Structure and Function - Catalytic Domains** (*David Wilson* / Tracey Gloster / Anna Larsson / Mirjam Czjzek)
- **Glycoside Hydrolase Structure and Function - CBMs and X-Domains** (*Roy Doi* / Bill Willats / Wade Abbott / Elodie Gaulin)
- **Prokaryote Genomics** (*Yuval Shoham* / Bernard Henrissat / Steven Hutcheson / Justin Sonnenburg / Phil Hugenholtz)
- **Eukaryote Genomics** (*Dan Cullen* / Amber Vanden Wymelenberg / Nina Aro)
- **Rational Design, Directed Evolution and Prospecting for Superior Enzymes** (*Henri-Pierre Fierobe* / Colin Mitchinson / Jonathon Caspi / Kevin Gray / Mark Nimlos)
- **Cellulases, Cellulosomes and Carbohydrate Active Enzymes in Engineered Processes** (*Tony Warren* / Mike Ladisch / Lee Lynd)

CERAMICS, SOLID STATE STUDIES IN
PROCTOR ACADEMY
ANDOVER, NH
AUG 5-10, 2007
RANDALL HAY, CHAIR
HELEN CHAN, VICE CHAIR

- **Complex Oxides: Issues and Challenges** (*Carol Handwerker* / Ivar Reimanis / Lynn Boatner)
- **High Temperature Structural Ceramics: Oxides - Processing and Properties** (Frank Zok / Reinhard Simon / Jay Lane)
- **SiC Ceramics: Applications and Issues** (*Triplicane Parthasarathy* / Toshihiro Ishikawa / Pirouz Pirouz)
- **Ultrahigh Temperature Ceramics** (*Kathleen Sevener* / David Marshall / John Halloran / Bill Fahrenholtz)
- **Deformation** (Erland Schulson)
- **Processing, Stability, and Applications of Non-Oxide Structural Ceramics** (*Greg Morscher* / Krishan Luthra / Tatsuki Ohji / Beth Opila)
- **Oxides: Nucleation and Growth** (*Bill Petuskey* / Geoff Fair / Laszlo Granasy)
- **Functional Ceramics: Modeling and Application** (*Greg Rohrer* / Gerbrand Ceder / Richard Gentilman / G. Scott Glaesemann)
- **Energy Sources** (*Randy Hay* / Ken Deffeyes)

CHEMICAL OCEANOGRAPHY
TILTON SCHOOL
TILTON, NH
AUG 5-10, 2007
EDWARD BOYLE, CHAIR
ROBERT ALLER, VICE CHAIR

- **Organic Geochemistry: Molecular Identification and Compound-Specific 14C**
- **Ocean Productivity, CO2 and Ocean Acidification**
- **Geochemical Paleoclimate**
- **Nutrients**
- **Trace Metal Interactions with Organisms**
- **Sediment Geochemistry**
- **Technology / Sensors / New Analytical Methods**
- **Stable Isotopes**
- **Gases**

CHEMICAL SENSORS & INTERFACIAL DESIGN
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 29-AUG 3, 2007
ANTHONY COLEMAN, CHAIR
MATTHEW COOPER, VICE CHAIR

- **Interfacing Molecular Molecular Recognition to Sensors**
  (*Anthony W. Coleman* / A.P. de Silva / Marius Andruh)
- **New Interfacial Materials - Porous and Non-Porous Solids**
  (*Scott Dalgrano* / John Ripmeester / Mohamed Eddaoudi / Dongwhan Lee)
- **Label Free Sensors 1**
  (*Reginald Penner* / John Parkes / Jiri Homola)
- **Label Free Sensors 2**
  (*Edward Zellers* / Israel Rubenstein / Luke Lee / Brian Cunningham)
- **Interfaces for Bio-Sensors**
  (Thomas Schrader / Yong-Tae Chang)
- **Array Technologies for Interfacial Construction**
  (*Jiri Janata* / David Reinhoudt / Sebastien Vidal / Chad Mirkin)
- **Short Talks - Selected Posters**
  (*Matthew Cooper*)
- **Integrated Sensor Systems**
  (*Hank Wohltjen* / Cindy J. Bruckner-Lea / Nate Lewis / Tim Gibson)
- **New Interfaces - From Academia to Industry**
  (*Lisa Hall* / Mary Reppy / Herve Perron)

CHROMOSOME DYNAMICS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
AUG 12-17, 2007
N. PATRICK HIGGINS, CHAIR
JULIA COOPER, VICE CHAIR

- **Keynote Talk: Control of Transcription Involves Topo II, Phased Nucleosomes, and DNA Repair**
  (Joeff Rosenfeld)
- **Tracking Chromosome Movement *In Vivo***
  (Jan Ellenberg / Nancy Kleckner / Alan Grossman / Stuart Austin / David Sherratt)
- **Coordinating Repair, Replication, and Recombination**
  (Sue Lovett / Kenneth Kreuzer / Susan Forsburg / Steve Bell)
- **Mechanisms of Chromosomal Attachment**
  (Frank Uhlmann / Barb Funnell / Ken Gerdes / Jeff Errington)
- **Marking and Checking Chromosome Behavior**
  (Ted Weinert / Gary Karpen / Rolf Sternglanz / Gary Karpen)
- **Controlling Steps in Segregation**
  (Scott Hawley / Donald Cleveland / Abby Dernburg / Sigal Ben-Yehuda / Terry Orr-Weaver)
- **Muscling DNA Around**
  (John Marko / James Berger / Reid Johnson)
- **Telomeres and Chromosome Evolution**
  (Ginger Zakian / Julie Cooper / Rachel O'Neill / James Haber)

COASTAL OCEAN MODELING
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 17-22, 2007
FRANCISCO WERNER, CHAIR
RICHARD SIGNELL, VICE CHAIR

- **Integration of Modeling and Observing Systems**
  (*Huijie Xue* / Nadia Pinardi / John Wilkin)
- **Bio-Physical Modeling**
  (*Charles Hannah* / Margaret McManus / Marjorie Friedrichs / Elizabeth North)
- **Atmosphere-Ocean Interaction**
  (*Julie Pullen* / Fabrice Ardhuin / Carol Anne Clayson)
- **Data Assimilation**
  (*Philip Bogden* / Emanuel DiLorenzo / Herman Gerritsen / Pierre De Mey)
- **Model Coupling and Adaptive Grids**
  (*John Wilkin* / Timothy Campbell / Matthew Piggott)
- **Hurricane / Severe Storm Modeling**
  (*Frank Aikman* / Donald Resio / Shuyi Chen / Rick Luettich)
- **Skill Assessment**
  (*Daniel Lynch* / Charles Stock / Roger Proctor)
- **Sediment Transport and Geomorphological Modeling**
  (*Richard Signell* / Jan Adriaan (Dano) Roelvink / Carl Friedrichs / Tian-Jian (Tom) Hsu)
- **Multiscale Modeling**
  (*Mark Stacey* / Alberto Scotti / Oliver Fringer)

CHEMISTRY EDUCATION RESEARCH & PRACTICE
BATES COLLEGE
LEWISTON, ME
JUN 24-29, 2007
CHRISTOPHER BAUER, CHAIR
THOMAS GREENBOWE, VICE CHAIR

- **Interacting with the Nano World**
  (*Robert Lichter* / Loretta Jones / Gail Jones)
- **Particulate Representation**
  (*Michael Abraham* / Robert Tinker / Vincente Talanquer / Barbara Gonzales)
- **Investigative Approaches**
  (*Susan Lewis* / Kevin Dunbar / Chris Rasmussen)
- **Student Thinking and Performance**
  (*Melanie Cooper* / Stacey Lowery Bretz / Philip Sadler / Mare Taagepera)
- **Curricula in Context**
  (*Jerry Bell* / Peter Nentwig / James Hutchison)
- **Epistemology and Knowledge Construction**
  (*Marcy Towns* / William Harwood / David Hammer / Michael Klymkowsky)
- **Student Problem Solving**
  (*Diane Bunce* / Norbert Pienta / Chandralekha Singh)
- **Learning Environments**
  (*Maria Oliver-Hoyo* / David Yaron)
- **Learning within Cultural Contexts**
  (*Thomas Greenbowe* / Amy Shachter / Gabriela Weaver)

CLUSTERS, NANOCRYSTALS & NANOSTRUCTURES
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 29-AUG 3, 2007
A. WELFORD CASTLEMAN JR., CHAIR
HELLMUT HABERLAND &
DAVID NORRIS, CO-VICE CHAIRS

- **Molecular Electronics**
  (*Jim Heath* / Stan Williams / Mark Ratner)
- **Catalysis**
  (*Vlasta Bonacic-Koutecký* / Peter Armentrout / Tamotsu Kondow)
- **Clusters and Materials**
  (*Atsushi Nakajima* / Shiv Khanna / Koji Kaya)
- **Cluster Reactivity**
  (*Martin Jarrold* / Ori Cheshnovsky / Manfred Kappes / Helmut Schwarz)
- **Characterization**
  (Joel Parks / Paul Weiss)
- **Photonics and Optical Interactions**
  (*Mike Duncan* / Mostafa El-Sayed / Lou Brus / George Schatz)
- **Nanostructures**
  (*Uzi Landman* / Catherine Brechignac / Nobuyuki Nishi)
- **Cluster Deposition**
  (*Wolfgang Harbich* / Mike White / Scott Anderson / Karl-Heinz Meiwes-Broer)
- **Cluster Properties**
  (*Puru Jena* / Kit Bowen / Lai-Sheng Wang)

COLLAGEN
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 22-27, 2007
DAVID BIRK, CHAIR
LEENA BRUCKNER-TUDERMAN, VICE CHAIR

- **Collagens: Molecular Structure & Assembly**
  (*Billy Hudson* / Barbara Brodsky / Jamshid Khoshnoodi / Shireen Lamande)
- **Regulation of Collagen: Transcription, Splicing and Trafficking**
  (*Linda Sandell* / Audrey McAlinden)
- **Collagen-Protein Interactions**
  (*Magnus Hook* / Richard Farndale)
- **Supramolecular Assemblies & Interactions in the Matrix**
  (*Peter Bruckner* / Jean Schwarzbauer / Daniela Villone / Markus Ruegg)
- **Extracellular Matrix Processing and Turnover**
  (*Daniel Greenspan* / Suneel Apte / Luisa Iruela-Arispe / Karl Kadler)
- **Genetics and Collagens**
  (*Kathy Cheah* / Pui-Yan Kwok / Danny Chan)
- **Cell-Matrix Interactions**
  (*Donald Gullberg* / Beate Eckes / Wolfgang Vogel / Taina Pihlajaniemi)
- **Collagen Diseases & Animal Models**
  (*John Bateman* / Brendan Lee / Francesco Ramirez)
- **Tissue Engineering & Regenerative Medicine**
  (*Vladimir Mironov* / Nicolas L'Heureux / Peter Lelkes / Richard Visconti)

COMBINATORIAL CHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 3-8, 2007
DARYL SAUER, CHAIR
PAUL HANSON, VICE CHAIR

- **New Technologies and Drug Discovery** (*Daryl Sauer* / Tom Beattie / Jim Summers / Steve Street)
- **Organic / Bio-Organic Chemistry** (*Oliver Kappe* / Stephen Martin / Bruce Lipshutz / Valery Folkin)
- **Libraries for Chemical Biology** (*Kip Guy* / Ben Cravatt / Doron Greenbaum / Jack Taunton / Jeremy Mallari)
- **Academic Combichem / Library Generation** (*A. Ganesan* / Ian Baxendale / Sergy Kozmin / Dave Bergbreiter / Nikki Pohl)
- **Enabling Technologies in Drug Discovery** (*Paul Wiedeman* / Mark Ladlow / Craig Lindsley / Steve Haswell)
- **NIH Roadmap Projects** (*John Schwab* / James Panek / Jeff Aube / Jared Shaw / Peter Wipf)
- **Case Studies 1: Medicinal Chemistry** (*Craig Lindsley* / Scott Wolkenberg / Andrew Combs / Joe Salvino)
- **Case Studies 2: Medicinal Chemistry** (*Joe Salvino* / Chris Sarko / Jim Leahy / Ron Dolle / Ralph Rivero)
- **Structural Approaches and Drug Design** (*Philip Hajduk* / Rod Hubbard / Jonathan Moore / Daniel Wyss / M. Pellecchia)

COMPUTER AIDED DRUG DESIGN
TILTON SCHOOL
TILTON, NH
JUL 29-AUG 3, 2007
RICHARD LEWIS, CHAIR
BRIAN SHOICHET, VICE CHAIR

- **Fragment-Based Screening** (Jim Wells / Phillip Hajduk)
- **Chemical Information & Target ID I** (Peter Willett / Bobby Glenn / Paul Clemons)
- **Chemical Information & Target ID II** (Andrew Hopkins)
- **Protein-Protein Interface Inhibitors** (Lynne Regan / Shoameng Wang)
- **New Advances in ADME** (Franco Lombardo)
- **Binding Affinity and Flexibility** (Mike Gilson / Arieh Warshel / Ivet Bahar)
- **Advances in Membrane Proteins Structures** (Robert Stroud / Krzysztof Palczewski)
- **Docking & Scoring** (Ruben Abagyan / Matt Jacobson / Marcel Verdonk)
- **Energetics and Drug Design** (Bill Jorgensen)

CONDENSED MATTER PHYSICS
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
AUG 19-24, 2007
ROBERT MAGERLE, CHAIR
DAVID NELSON, VICE CHAIR

- **Molecular Electronics**
- **Organic/Inorganic Interfaces**
- **Bioinspired Materials**
- **Morphology of Complex Structures**
- **Self-Assembled Superstructures**
- **Nanotubes and Nanoparticles**
- **Photonic Materials**
- **Pattern Dynamics**

DETECTING ILLICIT SUBSTANCES: EXPLOSIVES & DRUGS
BIG SKY RESORT
BIG SKY, MT
SEP 16-21, 2007
MATTHEW BROOKES &
AMY WATERS, CO-CHAIRS
LOUIS WASSERZUG, VICE CHAIR

- **New Concepts for Detection: Emerging Science and Technology** (*Dave Atkinson*)
- **Systems Approaches and Technology Integration** (*Mark Embrechts*)
- **Forensics and Chemical Surveillance** (*Sean Doyle*)
- **Humanitarian Demining** (*Claudio Bruschini*)
- **Novel Explosives** (*Shabana Haque*)
- **People Screening** (*Barry Smith*)
- **Baggage Screening** (*Harry Martz*)
- **Cargo and Vehicle Screening** (*Jaap de Ruiter*)
- **Special Session: Graduate Student Presentations** (*Lou Wasserzug*)

DEVELOPMENTAL BIOLOGY
PROCTOR ACADEMY
ANDOVER, NH
JUN 24-29, 2007
STEPHEN COHEN, CHAIR
ALEXANDER SCHIER, VICE CHAIR

- **Asymmetry and CNS** (*Stephen Cohen*)
- **Signaling, Morphogenesis and Patterning** (*Olivier Pourquie*)
- **Evolution and CNS** (*Eric Davidson*)
- **Growth Control** (*Norbert Perrimon*)
- **Genomics / Regulatory Networks** (*Ruth Lehmann*)
- **Organogenesis** (*Alex Schier / Laura Johnson*)
- **Stem Cells / Regeneration** (*Elizabeth Robertson*)

DRUG METABOLISM
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 8-13, 2007
JAE LEE, CHAIR
TIMOTHY TRACY, VICE CHAIR

- **Keynote Speaker: Bioactivation in Drug Metabolism. How Far Have We Come in Understanding the Phenomenon?** (Tom Baillie)
- **Non-CYP Enzymes and Oxidative Metabolism** (*Christine Beedham* / Christine Beedham / Enrico Garratini / Vasilis Vasiliou / John Cashman)
- **Impact of Protein-Protein Interaction on Metabolism** (*Wayne Backes* / Grover Paul Miller / Byron Kemper / Wayne Backes)
- ***In Vivo* Relevance of *In Vitro* Transporter Tools** (*Rommel Tirona* / Jose Manautou / Rommel Tirona / Richard Kim)
- **Transporter DDI; Pharmacological Ramification** (*Erin Schuetz* / Joe Polli / Jash Unadkat / John Schuetz)
- **The Innate Immune System and Idiosyncratic Drug-Induced Liver Toxicity** (*Robert Roth* / Neil Kaplowitz / Patricia Ganey / Hisham Hamadeh / Edward T. Morgan)
- **Selected Presentation from the Poster Session** (*Henry Strobel*)
- **ADME Computational Models** (*Scott Boyer* / Ulf Norinder / Yvonne Martin / Tudor Oprea / Scott Boyer)
- **Disposition and PK/PD of Biologics** (*David Lau* / Paul Fielder / Honghui Zhou / Kamesh Kuchimanchi)

DYNAMICS AT SURFACES
PROCTOR ACADEMY
ANDOVER, NH
AUG 12-17, 2007
BRET JACKSON, CHAIR
SYLVIA CEYER, VICE CHAIR

- **Scattering from Liquids** (*John Morris* / Gil Nathanson / David Nesbitt)
- **State-to-State Dynamics** (*Didier Lemoine* / Alec Wodtke / Geert-Jan Kroes / Rainer Beck)
- **Adsorbate Dynamics** (*Kristen Fichthorn* / Andrew Jardine / Ellen Backus)
- **Non-Adiabatic Effects** (*John Tully* / Karina Morgenstern / Mats Persson / Christian Frischkorn)
- **Dynamics of Desorption** (*Stephen Holloway* / Phil Cohen / Peter Saalfrank)
- **Ultrafast Dynamics** (*Tony Heinz* / Y. Ron Shen / Hrvoje Petek / Bradley Siwick)
- **Water at Interfaces** (*Mary Shultz* / Geri Richmond / Gregory Kimmel)
- **Nano-Scale Structures** (*Dinko Chakarov* / Tamar Seideman / Jason Crain / Andrew Rappe)
- **Young Investigator Program** (*Bruce Kay*)

ELASTIN & ELASTIC FIBERS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 29-AUG 3, 2007
ELAINE DAVIS, CHAIR
ANTHONY WEISS, VICE CHAIR

- **Molecular Structure and Properties of Elastin**
  (*Robert Mecham* / Régis Pomès / Tony Tamburro / Anthony Weiss)
- **Microfibril Ultrastructure and Assembly**
  (*Cay Kielty* / Clair Baldock / Penny Handford / Robert Mecham / Dieter Reinhardt)
- **Evolution and Functional Analysis of Elastic Fiber Proteins in Non-Mammalian Models**
  (*Fred Keeley* / Stephen Ekker / Bruce Vogel)
- **Elastic Fiber Assembly**
  (*Charlie Little* / Cay Kielty / Rocky Tuan)
- **Regulation of Growth Factors and Cell Function by Elastic Fiber Proteins**
  (*Lynn Sakai* / Giorgio Bressan / Dan Rifkin)
- **Heritable Diseases of the Vascular System: Basic Science and Therapeutic Advances**
  (*Dianna Milewicz* / Hal Dietz / Robert Thompson)
- **Elastic Fiber Function in Skin Development, Disease and Aging**
  (*Zsolt Urban* / Anne De Paepe / Alex Hinek / Violetta Iotsova-Stone)
- **Elastic Fiber Pathogenesis in Destructive Diseases of the Lungs**
  (*Marlene Rabinovitch* / Richard Bland / Ronald Goldstein / Steve Shapiro)
- **New Advances in Elastogenic Biomaterials and Bioengineering**
  (*Anthony Weiss* / Laura Niklason / Naren Vyavahare / Joyce Wong)

ELECTRON DISTRIBUTION & CHEMICAL BONDING: DYNAMICS AND DENSITIES
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 1-6, 2007
CARLO GATTI, CHAIR
DYLAN JAYATILAKA, VICE CHAIR

- **Where Are We Now, Where Are We Going?**
  (*Robert Stewart* / W.H. Eugen Schwarz / Mark Spackman)
- **Time Resolved Spectroscopy, Structure and Bonding: The Present**
  (*Claude Lecomte* / Philip Coppens / R.J. Dwayne Miller / Majed Chergui)
- **Time Resolved Spectroscopy, Structure and Bonding: The Future**
  (*Jochen Schneider* / Massimo Altarelli / Jerry Hastings / Henry Chapman)
- **High Throughput or Quality: Alternative Paths for X-ray Diffraction**
  (*Bo Iversen* / Alan Pinkerton / Mike Probert / Hans-Beat Buergi)
- **New Techniques and Tools for Structure, Bonding and Properties in Biology**
  (*Sine Larsen* / Pieter Glatzel / Chrif Matta)
- **Toward Charge Densities for Proteins: Which Database to Use? Will Biologists Care?**
  (*Paul Popelier* / Alberto Podjarny / Christian Jelsch / Pauline Dominiak / Birger Dittrich)
- **Progresses in Electron Diffraction**
  (*Kenji Tsuda* / Chong-Yu Ruan / Jesper Friis)
- **Chemical Concepts from Electron Density: Theory vs. Experiment**
  (*Richard Bader* / Wolfgang Scherer / Miguel A. Blanco / Louis Farrugia)
- **Densities, Density Matrices and Wavefunctions (in honor of V.H. Smith)**
  (*Ajit Thakkar* / Wolf Weyrich / David Mazziotti)

ENZYMES, COENZYMES & METABOLIC PATHWAYS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 8-13, 2007
SQUIRE BOOKER &
NIGEL RICHARDS, CO-CHAIRS
LIZBETH HEDSTROM &
NICOLE SAMPSON, CO-VICE CHAIRS

- **In Vivo Approaches to Monitoring Enzyme Action and Metabolic Pathways**
  (*Paul Adams* / Erin O'Shea / Sunney Xie)
- **Novel Metabolic Pathways**
  (*Barbara Gerratana* / John Cronan / Joseph P. Noel / David Sherman)
- **Mechanisms of Post-Translational Modification**
  (*Philip Cole* / Raymond Trievel / Stuart Licht / Dorothy Beckett)
- **Enzymology of Oxygen Activation**
  (*Judith Klinman* / Wilson Francisco / Astrid Gräslund / Justine Roth / John Lipscomb)
- **Tunnels Holes and Substrate Channeling**
  (*Frank Raushel* / Thomas Leyh / Osnat Herzberg / Dieter Söll)
- **Enzymes in Cofactor Biosynthesis, and Mechanisms of Cofactor Action**
  (*W.W. Cleland* / Vahe Bandarian / Bruce Palfey / Marie Alda Gilles-Gonzalez / Dieter Jahn)
- **Metallo-Cofactors in Enzyme Reactions**
  (*Anne-Frances Miller* / Markus Ribbe / Marty Bollinger / Dianne Newman)
- **Enzymes in Disease**
  (Peter Tummino / Clifton Barry / Craig Townsend / Dave Percival)
- **Frontiers in Enzymology**
  (*JoAnne Stubbe* / Tadhg Begley / Christopher Walsh)

ELASTOMERS, NETWORKS & GELS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 15-20, 2007
H. HENNING WINTER, CHAIR
JUDIT PUSKAS, VICE CHAIR

- **Elastomers**
  (James Mark / Claude Cohen)
- **Reinforced Networks**
  (Takeji Hashimoto / Robert K. Prud'homme / Francois Boue)
- **Rheological Properties**
  (Gregory B. McKenna / Gareth McKinley)
- **Biological and Biomedical Network Polymers**
  (Paul Janmey / Wolfgang Losert / Christopher N. Bowman)
- **Functional Networks**
  (Walter Richtering / Annette Schmidt)
- **Chain Dynamics**
  (Kay Saalwaechter / Jens-Uwe Sommer / Eric Furst / Madeleine Djabourov)
- **Gels**
  (Surita Bhatia / Moshe Gottlieb)
- **Elastomer Synthesis**
  (Katsutoshi Haraguchi / Krzysztof Matyjaszewski / Wayne Cook / Judit Puskas)
- **Outlook**
  (Richard Stein)

ELECTRONIC MATERIALS, CHEMISTRY OF
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 22-27, 2007
CHRISTOPHER CHIDSEY &
GARY TAYLOR, CO-CHAIRS
JILLIAN BURIAK &
CHRISTOPHER MURRAY, CO-VICE CHAIRS

- **Semiconductor Nanoelectronics: What's Needed for Dense Circuits Below 20nm?**
- **Advanced Materials for Nanoelectronics**
- **Leading-Edge Packaging Technology**
- **Organic Molecular Architectures**
- **Adventures in Nanoplasmonics**
- **Growth and Properties of 1D Semiconductor Nanostructures**
- **Self-Assembled Nanostructures**
- **Beyond Silicon Photovoltaics**
- **Carbon-Based Electronic Materials**

EPIGENETICS
HOLDERNESS SCHOOL
PLYMOUTH, NH
AUG 5-10, 2007
ANNE FERGUSON-SMITH &
STEVEN JACOBSEN, CO-CHAIRS
UELI GROSSNIKLAUS &
JEANNIE LEE, CO-VICE CHAIRS

- **Histone Modifications and Variants**
  (*Sarah Elgin* / Steve Henikoff / Hiten Madhani / Karolin Luger / Terry Magnuson / Justin Goodrich)
- **The Dynamic Nucleus**
  (*Jasper Rine* / David Spector / Edith Heard / Peter Fraser / En Li / Vincenzo Pirotta / Ting Wu)
- **Epigenomics**
  (*Steve Jacobsen* / Bradley Bernstein / Ian Dunham / Rob Martienssen / Peter Jones)
- **The Roles of RNA I & II**
  (*Bill Kelly* / Marjori Matzke / David Baulcombe / Phillip Zamore / Bob Kingston / Vikki Chandler / Craig Pikaard / Shiv Grewal / Denise Barlow)
- **DNA Methylation**
  (*Jörn Walter* / Eric Selker / Tim Bestor / Hiro Sasaki / Judith Bender / Xiaodong Cheng)
- **Imprinting, Dosage Compensation and Chromosomal Mechanisms**
  (*Emma Whitelaw* / Ueli Grossniklaus / Marisa Bartolomei / Jeannie Lee / Barbara Meyer / Jim Birchler)

- **Epigenetics in Developmental Processes** (*Tomoko Kaneko-Ishino* / Renato Paro / Rudolph Jaenisch / Laura O'Neill / Azim Surani / Wolf Reik)
- **Epigenetics and Disease** (*Amar Klar* / Olivier Voinnet / Asifa Akhtar / Steve Baylin / Mike Higgins)
- **Epigenetics, Environment and Evolution** (*Jean Finnegan* / Phil Avner / Eric Richards / Rick Amasino)

EPITHELIAL DIFFERENTIATION & KERATINIZATION
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 29-AUG 3, 2007
G. PAOLO DOTTO, CHAIR
PIERRE COULOMBE, VICE CHAIR

- **Global Approaches** (E. Fuchs / N. Perrimon / S. Schreiber)
- **Development and Cancer** (A. Dlugosz / S. Millar / F. Watt / A. Balmain / B. Edgar)
- **Stem Cells and Gene Therapy** (G. Cotsarelis / Y. Barrandon / M. DeLuca)
- **Transcription** (D. Roop / P. Chambon / H. Chang / E. Wagner / M. Brown)
- **Issue Rising Session I** (Speakers from the floor)
- **Differentiation and Signaling** (H. Baden / P. Khavari / P. Coulombe / W. Wahli / H. Timothy)
- **Issue Rising Session II** (Speakers from the floor)
- **Cell Adhesion and Morphogenesis** (K. Green / A. Christiano / C.M. Chuong / R. Faessler / R. Kopan)
- **Skin as an Integrated Organ** (M. Herlyn / L. Coussens / S. Werner)

EVOLUTIONARY & ECOLOGICAL FUNCTIONAL GENOMICS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 8-13, 2007
GREG WRAY, CHAIR
SCOTT EDWARDS, VICE CHAIR

- **Interactions Between Species** (Sarah Via / Phillipe Reymond)
- **Evolution of Regulatory Networks** (Mike Eisen / Julio Collado-Vides / Eddie Holmes)
- **Responses to Stressors** (Audrey Gasch / Theodore Morgan)
- **Speciation** (Hans Hoffman / Mohamed Noor / Leonie Moyle / Craig Albertson)
- **Physiological Ecology** (Doug Crawford / Adam Marsh)
- **Genomic Architecture of Genetic Variation** (Marie-Anne Felix / David Rand)
- **Sexual Selection** (Robert Brooks / Owen McMillan)
- **Reconstruction and Analyses of Ancestral Sequences** (Matheiu Blanchette / Belinda Chang / Eric Gaucher)
- **Transcription and Evolution** (Rachel Brem / Sergy Nuzhdin)

EXCITATORY SYNAPSES & BRAIN FUNCTION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 10-15, 2007
ROBERT MALENKA, CHAIR
CHRISTOPHE MULLE &
GARY WESTBROOK, CO-VICE CHAIRS

- **Experience-Dependent Plasticity (Keynote Lectures)** (Mark Bear / Hollis Cline)
- **Presynaptic Mechanisms** (*Craig Garner* / Nils Brose / Hugo Bellen / Tom Sudhof / Rob Edwards)
- **Glia and Synaptic Function** (Craig Jahr / Stephane Oliet / Shumin Duan)
- **Technology Advances** (Pam England / Karl Deisseroth / Alla Karpova / Daniele Choquet)
- **Development** (Vivian Budnik / Anirvan Ghosh / Lu Chen / Sari Lauri)
- **Structure and Spines** (Jesse Kastrup / Mark Mayer / Wen-Biao Gan / Bernardo Sabatini)
- **Disease** (*Julie Kauer* / Jane Sullivan / Marina Wolf / Jeff Conn)
- **Cell Biology** (Shigeo Okabe / Bob Wenthold / Morgan Sheng / Rick Huganir)
- **Synaptic Plasticity** (Wade Regher / Allison Barth / Christophe Mulle / Graham Collingridge)

FERTILIZATION & ACTIVATION OF DEVELOPMENT
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 15-20, 2007
GEORGE GERTON, CHAIR
ALBERTO DARSZON, VICE CHAIR

- **Post-Testicular Maturation of Sperm** (*Patricia Cuasnicu* / Daniel Johnston / R. John Aitken / Mariana F. Wolfner)
- **Role of the Female Reproductive Tract in Gamete Interactions** (*Steven L'Hemault* / Susan Suarez / Tadashi Baba)
- **Chemotaxis and Sperm Motility** (Doug Chandler / Michael Miller / Debbie O'Brien)
- **Sperm-Oocyte Extracellular Matrix Interactions** (*Daniel Hardy* / William J. Snell / Jurrien Dean)
- **Sperm Signaling** (*Alberto Darszon* / Pablo Visconti / Claudia Tomes)
- **Oocyte Arrest and Egg Activation** (*Janice Evans* / Karl Swann / Lynda McGinnis / Alexei V. Evsikov)
- **Polarity of Egg and Early Embryo** (*Carmen Williams* / Takashi Hiiragi)
- **Gametes, Early Embryos, and Epigenetics** (Rabindranath De La Fuente / Kevin Eggan)
- **Chairs and a Round Table: Past, Present, Future of Fertilization and Activation of Development** (*George Gerton* / Previous chairs of conference in attendance)

FLORAL & VEGETATIVE VOLATILES
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
OCT 7-12, 2007
ERAN PICHERSKY, CHAIR
WITTKO FRANCKE, VICE CHAIR

- **Roles of Plant Volatiles in Human Affairs** (*Steve Goff* / Efraim Lewinsohn / Roman Kaiser / Harry Klee / Fred Provenza)
- **Vegetative Volatiles: Molecular Ecology and Metabolomics** (*Ted Turlings* / Jonathan Gershenzon / Nicole Van Dam / Ian Baldwin / Junji Takabayashi)
- **Vegetative Volatiles: Behavioral Ecology** (Marcel Dicke / Monika Hilker / Joop van Loon / Matthias Held / Consuelo De Moraes)
- **Floral Volatiles: Generalized and Food/ Reward-Based Pollination** (*Florian Schiestl* / Candance Galen / Steffan Dotterl / Tia-Lynn Ashman / Steven Johnson)
- **Floral Volatiles: Specialized and Sexually Deceptive Pollination, and Obligate Mutualism** (*Robert Raguso* / Olle Pelmyr / Rod Peakall / Marcus Stensmyr)
- **Chemistry and Biochemistry of Plant Volatiles: Molecules, Biosynthetic Pathways, and Enzymes** (*Jorge Bohlmann* / Natalia Dudareva / Robert Schuurink / Eyal Fridman / Amy Marshall-Colón / Dorothea Tholl / Wittko Francke / Wilfried Schwab / Harro Bouwmeester)
- **Techniques and Methodologies for Studying Plant Volatiles** (*Dorothea Tholl* / Wilhelm Boland / Francesco Loreto / Armin Hansel / Anna-Karin Borg-Karlson / Anita Marsaioli)

FUEL CELLS
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 22-27, 2007
BRYAN PIVOVAR &
TOMOYUKI TADA, CO-CHAIRS
STEPHEN CAMPBELL &
MATTHEW MENCH, CO-VICE CHAIRS

- **Fuel Cells - Status and Future** (*Bryan Pivovar* / *Tomoyuki Tada* / Koichi Kojima / Martin Apple)
- **Membrane Electrode Assemblies** (*Jeremy Meyers* / Mike Yandrasits / Seiho Sugawara / Hubert Gasteiger)
- **Catalysis** (*Tom Zawodzinski* / Matt Neurock / Manos Mavrikakis / Fred Wagner)
- **Advanced Characterization Techniques** (Hiroshi Jinnai / Hideto Imai / Andrzej Wieckowski)
- **Polymer Electrolyte Membranes** (Takeo Yamaguchi / Michael Guiver)
- **Carbon Supports** (Paolina Atanassova)
- **Water Transport** (Mike Hickner / Olivier Diat)
- **Advanced Concepts / Future Technology** (John Varcoe / Ken-ichiro Ota)

GENETIC TOXICOLOGY
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
JUL 29-AUG 3, 2007
ANTONY CARR, CHAIR
SAMUEL WILSON, VICE CHAIR

- **Keynote Talk 1: Responses to Oxidative DNA Damage**
  (Ben van Houten)
- **Keynote Talk 2: Cancer Risk and Chernobyl**
  (Richard Wakeford)
- **Endogenous and Induced DNA Damage**
  (*Sam Wilson* / John Essigmann / Peter McKinnon / Marcus Lobrich / Aidan Doherty / Jo Jiricny / Keith Caldecott / Peter Karren / Cynthia McMurray)
- **Mutagenesis and DNA Repair**
  (*Tom Kunkel* / Greg Verdine / William Dunphy / Ohstura Niwa / Kevin Hiom / Peggy Hsieh / Travis Stracket)
- **Replication - Links to Genotoxicity**
  (*Ian Hickson* / Peter McGlynn / Helle Ulrich / Laurence Pearl / John Diffley / Thomas Helleday / Susan Gasser / Alan Lehmann / Ron Laskey)
- **Chromatin and Cell Fate Decisions**
  (*Steve Jackson* / Shigeki Miyamoto / Geoff Wahl / Karl-Peter Hopfner / Thanos Halazonetis / Kyunglae Myung / Jessica Downes)

HETEROCYCLIC COMPOUNDS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 24-29, 2007
ERIK SORENSEN, CHAIR
KARIN BRINER, VICE CHAIR

- **New Reactions and Ideas for the Synthesis of Heterocyclic Compounds I**
  (*Karin Briner* / Justin Du Bois / Melanie Sanford / Edwin Vedejs)
- **Novel Pericyclic Reactions for Syntheses of Heterocycles**
  (*George Sheppard* / Peter Jacobi / William Murray / Raymond Funk / Rick Danheiser)
- **New Catalytic Reactions for Heterocycle Synthesis I**
  (*Melissa Vasbinder* / Helené Lebel / Richmond Sarpong / Jeffrey Johnson)
- **New Reactions and Ideas for the Synthesis of Heterocyclic Compounds II**
  (*Christopher Vanderwal* / Brian Stoltz / Scott Edmondson / John Wolfe / Nicholas Magnus)
- **Innovative Concepts for Constructing Complex Heterocyclic Natural Products & Pharmaceutical Agents I**
  (*Rick Ewing* / Madeleine Joullié / Prashant Deshpande / Dirk Trauner)
- **Creative Advances in Syntheses of Complex Heterocyclic Natural Products**
  (*Brian Aquila* / Kathy Parker / Emanuel Theodorakis / James Panek)
- **New Catalytic Reactions for Heterocycle Synthesis II**
  (*Roger Hahn* / Eric Jacobsen / Scott Miller / David MacMillan)
- **Innovative Concepts for Constructing Complex Heterocyclic Natural Products & Pharmaceutical Agents II**
  (*Michael Miller* / Mohammad Movassaghi / Steve Colletti / Eun Lee / Phil Baran)
- **Insights into the Chemical Problems Posed by Structurally Complex, Heterocyclic Natural Products**
  (*Gregory Dake* / Gilbert Stork)

HIGH TEMPERATURE CORROSION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 29-AUG 3, 2007
W. JOE QUADAKKERS, CHAIR
JOHN NICHOLLS, VICE CHAIR

- **Microstructural Effects in Alumina Scale Growth**
  (B. Gleeson / G. Tatlock)
- **Oxidation Properties Of Pt Modified Aluminides**
  (S. Hayashi / V. Tolpygo)
- **Interfaces in High Temperature Corrosion Processes**
  (D. Young / P. Hou)
- **Corrosion in Chlorine Containing Environments**
  (M. Schütze / J.E. Svensson)
- **Water Vapour Effects on Oxidation Processes in Low- and High pO_2-Environments**
  (B. Pint / D. Naumenko)
- **Oxidation Issues in Solid Oxide Fuel Cells**
  (T. Maruyama / J. Zhu)
- **Materials for Very High Temperature Applications**
  (M. Barsoum)
- **Thermal Barrier Coating Systems**
  (M. Carlin)
- **High Temperature Materials for Energy and Heat Management in Automobiles**
  (P. Fallboehmer)

HORMONE ACTION IN DEVELOPMENT & CANCER
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 15-20, 2007
SHIUAN CHEN &
PAOLO SASSONE-CORSI, CO-CHAIRS
GAIL PRINS & KEVIN WHITE, CO-VICE CHAIRS

- **Keynote Talk 1: Nuclear Receptors - Metabolic Engineering and the Dawn of Synthetic Physiology**
  (*Ronald Margolis* / *John MacLachlan* / Ronald Evans)
- **Keynote Talk 2: Prostate Tumor - Microenvironment Interaction**
  (*Ronald Margolis* / *John MacLachlan* / Leland Chung)
- **Hormone and Cancer I**
  (*John Couse* / *Jose Russo* / Jianming Xu / Fazlul Sarkar / Wayne Tilley / Franky Chan)
- **Hormone and Stem Cells**
  (*Gail Prin* / *Raj Tekmal* / Max Wicha / Susan Kasper / Gail Risbridger)
- **Circadian/Metabolism**
  (*Paolo Sassone-Corsi* / *Maarten Bosland* / William Schwartz / Charles Weitz / Cheng Chi Lee / Richard Stevens)
- **Hormone and Development I**
  (*Kevin White* / *Lynn Riddiford* / Michael Mancini / Henry Krause / Joe Thornton)
- **Hormone and Cancer II**
  (*Chawnshang Chang* / *Suzanne Fuqua* / Gregory Brent / Thomas Burris / Hideo Honjo / Hsing-Jien Kung)
- **Epigenetics**
  (*Shuk-Mei Ho* / *Jerry Heindel* / Shelley Berger / Doug Ruden / Richard Pestell)
- **Hormone and Development II**
  (*Neeraja Sathyamoorthy* / *Gerhard Coetzee* / Hugh Taylor / David Sassoon / Caren Helbing)
- **Hormone Action / Translational Research**
  (*Angela Brodie* / Charles Perou)

HUMAN GENETICS & GENOMICS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 22-27, 2007
JAMES LUPSKI, CHAIR
EVAN EICHLER, VICE CHAIR

- **Keynote Talk 1: How Many Genes for a Complex Disease?**
  (Aravinda Chakravarti)
- **Keynote Talk 2: TBA**
  (Helen Hobbs)
- **Landscape-Setting Talks**
  (*Peggy Pericak-Vance*)
- **Human Genetic Disease - From Mendel to Complex Traits**
  (*Nicholas Katsanis* / Mike Green / Ying-Hui Fu)
- **Human Evolutionary Genetics**
  (*Pardis Sabeti* / Andrew Clark / Sara Tishkoff)
- **Human Chromosome Biology and Genome Dynamics**
  (*Huntington Willard* / Barbara Trask / Vivian Cheung / John Moran / Evan Eichler / Nigel Carter)
- **Beyond the Human Hapmap-Links Between Phenotype and Genotype**
  (*David Altshuler*)
- **New Genome Technologies**
  (*David Bentley* / Richard Gibbs / Eric Green)
- **Genome Structural Variation and Phenotype**
  (*James Lupski* / Sunil Ahuja / Art Beaudet)
- **Molecular Genetics and Therapeutics Of Human Genetic Disease**
  (*Hal Dietz* / Steve Warren / Mark Kay)

HYDROGEN-METAL SYSTEMS
COLBY COLLEGE
WATERVILLE, ME
JUL 8-13, 2007
CRAIG JENSEN & KLAUS YVON, CO-CHAIRS
ETSUO AKIBA &
GARY SANDROCK, CO-VICE CHAIRS

- **Intermetallic Hydrides**
  (Valerie Paul-Boncour / Yaroslav Filinchuk)
- **Yttrium and Lanthanum Hydride**
  (Akihilo Machida / Walter Wolf / Joachim Schoenes)
- **Hydrogen on Surfaces**
  (Klaus Christman / Adolf Winkler)
- **Defects**
  (Chris Van de Walle / Rosario Cantelli / Ryosuke Kadono)
- **Spectroscopy**
  (Stewart Parker / David Sholl / Hans Hagemann)
- **New Methods of Characterization**
  (Robin Gremaud / Ji-Cheng Zhao / Son-Jong Hwang)
- **Magnesium Hydride**
  (Pietra de Jongh / Hannes Jonsson)

- **High Capacity Hydrogen Storage Materials I**
(Per Erick Vullum / Tabbetha Dobbins / Ping Chen / Job Rijssenbeek)
- **High Capacity Hydrogen Storage Materials II**
(Yuko Nakamori / Chris Wolverton / Ewa Ronnebro / Tom Autrey)

INHIBITION IN THE CNS
COLBY COLLEGE
WATERVILLE, ME
JUL 22-27, 2007
CHRIS MCBAIN, CHAIR
HANNAH MONYER, VICE CHAIR

- **Keynote Talk 1: Inhibitory Cells and Circuits - A Personal View**
(Richard Miles)
- **Keynote Talk 2: Interneuron Hierarchies and Oscillatory Organization of Cell Assemblies**
(Gyorgy Buzsaki)
- **Development of Inhibitory Circuits**
(*Hannah Monyer* / Angelique Bordey / Gordon Fishell / Josh Huang / Rosa Cossart)
- **Structure and Function of $GABA_A$ and $GABA_B$ Receptors**
(Robert MacDonald / Cynthia Czajkowski / Neil Harrison / Bernard Bettler)
- **Inhibitory Circuits in the CNS**
(*Gianmaria Maccaferri* / Gyorgy Buzsaki / Massimo Scanziani / Pablo Castillo / Peter Jonas / Thomas Klausberger / Tams Freund / Alex Thomson / Ivan Soltesz)
- **GABA and Glycine Receptors**
(*Stefano Vicini* / Amy MacDermott / John Huguenard / Gabor Tamas / Lori McMahon)
- **GABA Receptor Modulation**
(*Stephen Moss* / Bryndis Bimir / Jamie Maguire / David Weiss)
- **Plasticity and Pathology of Inhibition**
(*Istvan Mody* / Dimitri Kullmann / Julie Kauer / Jean Claude Lacaille / David Lewis)

INORGANIC CHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 15-20, 2007
WILLIAM BUHRO, CHAIR
KIM JOHNSON, VICE CHAIR

- **Organometallic Chemistry**
(*Richard Kemp* / Teri Odom / Timothy Warren / Guy Bertrand)
- **Solid-State and Materials Chemistry**
(*Janet Braddock-Wilking* / Gregory Girolami / Alan Heyduk / Catalina Achim / Mark MacLachlan)
- **Supramolecular Chemistry**
(*Paul Sharp* / Kyoung-Shin Choi / Jonathan Nitschke / Andrew Borovik)
- **Nanoscience**
(*Sophia Hayes* / Michael Sailor / Anne-Frances Miller / Ana de Bettencourt)
- **Main-Group Chemistry**
(*William Buhro* / Evamarie Hey-Hawkins / Marina Petrukhina / William Tolman)
- **Catalysis**
(*Bahram Moasser* / Kimberly Johnson / Elena Rybak-Akimova)
- **Bioinorganic Chemistry**
(*George Stanley* / Thomas Brunold / Slavi Sevov / Jennifer Hollingsworth)
- **Coordination Chemistry**
(*Clifford Kubiak* / Kristin Bowman-James / Donald Darensbourg / Janet Morrow)
- **Celebrating Excellence**
(*Kimberly Johnson* / Robert Paine / Richard Schrock)

INTERIOR OF THE EARTH
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 10-15, 2007
GORAN EKSTROM, CHAIR
BRUCE BUFFETT, VICE CHAIR

- **The Continental Lithosphere: Where Did it Come From, Where Does it Go?**
(*Roberta Rudnick* / Peter Keleman / Adrian Lenardic)
- **The Asthenosphere I - What Is the Asthenosphere?**
(*Stan Hart* / Greg Hirth / Lars Stixrude / Shijie Zhong)
- **The Asthenosphere II - How Do the Lithosphere, Asthenosphere and Deeper Mantle Interact?**
(*Magali Billen* / Anne Davaille / Hans Keppler)
- **Oceanic Lithosphere from Ridge to Trench**
(*Donald Forsyth* / Robert Dunn / Robert Evans / Keith Priestley)
- **Anisotropy - Fabric Development, Maintenance, and Destruction**
(*Thorsten Becker* / James Gaherty / Andrea Tommasi)
- **Subduction Zones - What Goes Down and What Comes Up?**
(*Geoffrey Abers* / Karen Fischer / Katherine Kelley / Jason Phipps Morgan)
- **Why is the Transition Zone Important?**
(*Paul Tackley* / David Bercovici / Donald Weidner)
- **Deglaciation and Sea-Level Change - Earth's Response to Loading on Multiple Time Scales**
- **Unresolved Questions**
(*Barbara Romanowicz* / Geoff Davies / Marc Hirschmann)

LASER DIAGNOSTICS IN COMBUSTION
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
AUG 12-17, 2007
PAUL EWART, CHAIR
VOLKER SICK, VICE CHAIR

- **Hot Topics - Selected from Poster Contributions**
(*Volker Sick*)
- **High Speed Imaging**
(*Jonathan Frank* / Jay Smith / Walter Lempert / Jeremy Coupland)
- **Turbulent Combustion**
(*Marshall Long* / Rob Barlow / Andreas Dreizler)
- **Soot and Particulate Emissions**
(*Christof Schulz* / Angela Violi / Boris Kock / Pascale Desgroux)
- **Nonlinear Optical Techniques**
(*Bob Lucht* / Sukesh Roy / Peter Barker)
- **New Laser Sources and Techniques**
(*Tom Settersten* / Jun Ye / Richard Miles / Katharina Kohse-Höinghaus)
- **Biological Applications and Future Challenges**
(*Marcus Alden* / Jurgen Wolfrum)
- **Diode Laser-Based Techniques**
(*Mark Allen* / Ron Hanson / Johan Hult / Terrence Meyer)
- **Diagnostic Techniques for Engine Applications**
(*Doug Greenhalgh* / Scott Sanders / Thomas Seeger)

LIPIDS, MOLECULAR & CELLULAR BIOLOGY OF
WATERVILLE VALLEY RESORT
WATERVILLE VALLEY, NH
JUL 22-27, 2007
CHARLES MARTIN, CHAIR
DAVID RUSSELL, VICE CHAIR

- **Keynote Talk 1: Role of Structural Lipidomics in Genome Annotation**
(Christian Raetz)
- **Keynote Talk 2: Gene Deletions in Mice - Insights into Phosphatidylcholine Function**
(Dennis Vance)
- **Structure and Catalysis at the Lipid-Protein Interface**
(Stephen White / John Shanklin / Bill Dowhan / Charles Rock)
- **Lipid Dysfunction and Metabolic Disease**
(*Susanne Jackowski* / Gerald Shulman / Jean Schaffer / Jay Horton)
- **Lipid Metabolic Regulation**
(*Susan Henry* / Diego DeMendoza / George Carman / Russell DeBose-Boyd / Takanari Inoue)
- **Lipid Transport**
(John F. Oram / Judith Storch / Concetta DiRusso)
- **Lipid Diversity and Metabolic Engineering**
(*Teresa Dunn* / John Browse / Anthony Kinney / Henry Valentin / Naren Yadav)
- **Lipid Dynamics in Infection and Immunity**
(Alfred Bendelac / Christina Leslie / Dennis Voelker)
- **Fat Deposition and Turnover**
(Guenther Daum / Robert Farese / Dominique Langin / Karen Reue)
- **Regulation of Lipid Homeostasis**
(*Jean Vance* / James Ntambi / Dan Ory / Christoph Benning)

LIQUID CRYSTALS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 10-15, 2007
GREGORY CRAWFORD, CHAIR
PETER COLLINGS, VICE CHAIR

- **Imaging Devices**
- **Sensors**
- **Lasing and Photonic Bandgap Devices**
- **Bio-Inspired Materials**
- **Colloids, Self Assembly, and Molecular Aggregation**
- **Nanoparticle Dispersions and Carbon Nanotubes**
- **Synthesis and Characterization of New Liquid Crystals**
- **Theory, Modeling, and Computation**
- **Liquid Crystal Elastomers**
- **Liquid Crystal Ordering and Biological Function**

LIQUIDS, CHEMISTRY & PHYSICS OF
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 29-AUG 3, 2007
DAVID REICHMAN, CHAIR
STEVE GRANICK, VICE CHAIR

- **Complex Fluids**
  (Jay Groves / David Pine)
- **Charged Liquids/Polyelectrolytes**
  (John Weeks / Alfons van Blaaderen)
- **Glass Transition**
  (John Torkelson / Peter Harrowell / Ludovic Berthier)
- **Confined/Interfacial/Biological Fluids**
  (Jean-Francois Joanny / Seth Fraden / Nancy Levinger)
- **Dewetting/Hydrophobicity**
  (Bruce Berne / Shakar Garde / Francoise Brochard-Wyart)
- **Spectroscopy of Liquids**
  (Andrei Tokmakoff / Huib Bakker / David Blank)
- **Polymeric Liquids**
  (Liliane Leger / Ken Schweizer)
- **Simulation Studies**
  (Peter Rossky / Bernhardt Trout)

MAGNETIC RESONANCE
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 17-22, 2007
SHIMON VEGA, CHAIR
BEAT MEIER, VICE CHAIR

- **The GRC Where EPR and NMR Meet**
  (*Michael Mehring* / Jan Schmidt / Ray Freeman)
- **Order and Dynamics in Bio-Molecules**
  (*Kurt W. Zilm* / Stephan Grzesiek / Geoffrey Bodenhausen / Stanley Opella)
- **Non-Conventional Magnetic Resonance**
  (*Daniel P. Weitekamp* / Go Yusa / Michael Romalis / Arno Kentgens)
- **Bio-Solids NMR**
  (*Robert Tycko* / Jacob Schaefer / Chad Rienstra / Ann McDermott / Bernd Reif)
- **Sensitivity Enhancement**
  (*Malcolm H. Levitt* / Walter Kockenberger / Joachim Bargon / Robert G. Griffin)
- **NMR Methodology and Materials**
  (*Hans W. Spiess* / Dominique Massiot / Mei Hong / Zhehong Gan)
- **Magnetic Resonance Imaging**
  (*Lucio Frydman* / Aharon Blank / Warren S. Warren / Klaas Pruessmann)
- **Paramagnetic Resonance**
  (*Jack H. Freed* / Brian M. Hoffman / Gunnar Jeschke / Klaus-Peter Dinse / Oleg P. Poluektov)
- **NMR at Low Field**
  (*Beat Meier* / Alex Pines / Paul Callaghan)

MALARIA
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
SEP 9-14, 2007
KEVIN MARSH, CHAIR
CHETAN CHITNIS, VICE CHAIR

- **Keynote Talk 1: Global Distribution and Burden of Malaria**
  (Bob Snow)
- **Keynote Talk 2: Malaria and the Human Genome**
  (Dominic Kwiatkowski)
- **Severe Malaria**
  (*Charles Newton* / Richard Idro / Kamija Phiri / Ric Price / Kath Maitland)
- **Pathogenesis**
  (*Terrie Taylor* / Steve Kamiza / Sam Wassmer / Jay Berkley)
- **Drugs for Malaria**
  (*Nick White* / Alexis Nzila / Marian Warsame / Karen Barnes)
- **Malaria in Pregnancy**
  (*Brian Greenwood* / Pat Duffy / Clara Menendez / Rose McGready)
- **Novel Interventions**
  (*Ogobara Doumbo* / David Schellenberg / Badara Cisse / Simon Brooker)
- **Vectors**
  (*Janet Hemmingway* / Immo Kleinschmidt / Martin Donnelly / Paul Eggleston)
- **Vaccines**
  (*Pedro Alonso* / Peter Billingsley / Chetan Chitnis)
- **Going to Scale**
  (*Fred Binka* / Nick White / Marcel Tanner / Catherine Goodman / Ramanan Laxminarayan)

MAMMARY GLAND BIOLOGY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 10-15, 2007
STEVEN ANDERSON, CHAIR
CATHRIN BRISKEN, VICE CHAIR

- **Opening Address: Genes That Mediate Breast Cancer Metastasis - Why Tumor Cells Migrate to Specific Places**
  (*Steven M. Anderson* / Joan Massague)
- **Stem Cells in Mammary Gland Development and Tumorigenesis**
  (*Caroline M. Alexander* / Jeff Rosen / Max Wicha / Lothar Hennighausen)
- **Development of the Mammary Gland**
  (*Cathrin Brisken* / Jacqueline Veltmaat / Pam Cowin)
- **Cancer Models**
  (*William J. Muller* / Linda Schuler / Kathryn L. Schwertfeger / Alana Welm)
- **Translation to the Clinic**
  (*Adrian Lee* / Carlos Arteaga / Douglas Yee)
- **Tumor Metabolism - Warbrug Revisited**
  (*D. Joseph Jerry* / Paul M. Hwang / Valeria R. Fantin / William B. Kinlaw)
- **The Lactation Switch**
  (*Ian Mather* / Dean P. Edwards / Lewis Chodosh)
- **The Involution Switch**
  (*Terri Wood* / Darryl Hadsell / Christine Watson / Peter Henson)
- **Keynote Address: A Physiologist Looks and Mammary Gland Development and Function**
  (*Steven M. Anderson* / Margaret C. Neville)

MATRIX ISOLATED SPECIES, PHYSICS & CHEMISTRY OF
BATES COLLEGE
LEWISTON, ME
JUL 15-20, 2007
ARA APKARIAN, CHAIR
MARIO FAJARDO &
CHARLES WIGHT, CO-VICE CHAIRS

- **Matrix Isolation - Spectroscopy**
  (*Martin Vala* / Lester S. Andrews / Marilyn E. Jacox / William Graham)
- **Photochemistry**
  (*Hideo Tomioka* / Laurent Manceron / Zofia Mielke)
- **Quantum Hosts - Helium**
  (*Jussi Eloranta* / Andrey Vilesov / Kevin K. Lehmann)
- **Quantum Hosts - Solid Hydrogen**
  (*Mario E. Fajardo* / Yuan-Pern Lee / Robert J. Hinde / David T. Anderson / Takamasa Momose)
- **Photodynamics**
  (*Charles A. Wight* / Leonid Khriachtchev)
- **Dynamics (Time Resolved)**
  (*Ilya Goldschleger* / Nikolaus Schwentner / Mika Pettersson / Peter Hamm)
- **Novel Species**
  (*Rui Fausto* / Markku Rasanen / Mingfei Zhou / Benny Gerber)
- **Clathrates**
  (*Werner Klotzbuecher* / Kenneth Janda / Werner F. Kuhs / Kenneth D. Jordan / Keith Hester)
- **Ices**
  (*Sam Abrash* / Murthy S. Gudipati / Victoria Buch)

MATRIX METALLOPROTEINASES
IL CIOCCO
LUCCA (BARGA), ITALY
JUN 3-8, 2007
CARLOS LOPEZ-OTIN, CHAIR
CARL BLOBEL, VICE CHAIR

- **Matrix Metalloproteinases: An Evolving Field**
  (*Carlos Lopez-Otin* / Stephen Krane / Bill Parks / Amanda Fosang)
- **Matrix Metalloproteinases: Essential Regulators of Cell Behaviour**
  (*Agnes Noel* / Shahin Rafii / Luisa Iruela-Arispe / George Davis / Alicia G. Arroyo / Steve Weiss)
- **The Dual Roles of Matrix Metalloproteinases in Cancer**
  (*Steve Weiss* / Dylan Edwards / Lynn Matrisian / McGarry Houghton / Alex Strongin / Derek Radisky)
- **MMPs and Their Inhibitors: New Approaches to Old Problems**
  (*Gillian Murphy* / Robert Visse / Hyeong-Reh Kim / Steve van Doren / Chris Overall / Niels Behrendt / Motoharu Seiki / Greg Goldberg / Rama Khokha)
- **The Other Metalloproteinases: ADAMs, ADAMTSs and Beyond**
  (*Carl Blobel* / Suneel Apte / Joaquín Arribas / Dominique Alfandari / Claus Oxvig / Daniel S. Greenspan)
- **Matrix Metalloproteinases in Human Disease**
  (*Lynn Matrisian* / Eng H. Lo / Annie Pardo / Timo Sorsa / Massimo Federici / Peter Libby)

- **Matrix Metalloproteinases: A Structural Glimpse**
  (*Xavier Gomis-Ruth* / Wolfram Bode / Ulrich Baumann / Yoshinori Akiyama / Stefan Gerhardt / Soichi Takeda)
- **Towards a New Generation of Metalloproteinase Inhibitors**
  (*Chris Overall* / Vincent Dive / Seth Cohen / Dorothea Piecha / Mike Janusz / Roy Black / Bin-Bing S. Zhou)
- **Matrix Metalloproteinases: The Future Ahead**
  (*Carl Blobel* / Zena Werb)

MECHANISMS OF CELL SIGNALLING
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
SEP 16-21, 2007
JONATHAN CHERNOFF, CHAIR
CHRISTOPHER MARSHALL, VICE CHAIR

- **Keynote Talk: Integrins and Small GTPases - A Two-Way Street**
  (Martin Schwartz)
- **The Big Picture: Integrating GTPase Signal Transduction**
  (*Doug Lauffenberger* / Peter Nollau / Jason Haugh / Julian Downward / Channing Der)
- **GTPase Signaling: Subcellular Localization**
  (*Adrienne Cox* / Rick Horwitz / Michiyuki Matsuda / Klaus Hahn)
- **Small GTPases and the Regulation of Cell Division**
  (*Alan Hall* / Shuh Narumiya / Cayetano Gonzalez / Ian Macara)
- **Cell Polarity and Differentiation**
  (*Valerie Weaver* / Kodi Ravichandran / Tatsuo Kinashi)
- **Cell Adhesion/Migration**
  (*Chris Marshall* / Hans Bos / John Collard / Kriistiana Vuori)
- **Small GTPases: Organismal Biology and Development**
  (*Jeffrey Settleman* / Linda van Aelst / Andre Bernards / Georg Halder)
- **Small GTPases, Signaling, and Cancer**
  (*Dafna Bar-Sagi* / David Tuveson / Ed Manser / Frank Slack / John Sondek)
- **Signal Transduction-Based Therapeutics**
  (*Robert Abraham* / Lisa Henske / Yi Zheng)

MECHANISMS OF MEMBRANE TRANSPORT
TILTON SCHOOL
TILTON, NH
JUN 10-15, 2007
PETER MALONEY, CHAIR
AMY DAVIDSON, VICE CHAIR

- **Biophysical and Biological Principles**
  (*Peter Maloney* / Milton Saier, Jr / Werner Kuhlbrandt / H. Ronald Kaback)
- **ABC and E1E2 Transporters**
  (*Amy Davidson* / Heather Pinkett / David Gadsby / Kaspar Locher)
- **Crossing the Bilayer**
  (*Steve White* / Don Engleman / Shimon Schuldiner)
- **Gating and Conduction**
  (*David Gadsby* / Youxing Jiang / Rod MacKinnon / Gary Yellen)
- **Ion, Solute and Water Channels**
  (*Ching Kung* / Michael Maguire / Tamir Gonen / Chris Miller)
- **Selected Poster Talks**
  (*Chris Miller*)
- **Transporters**
  (*H. Ronald Kaback* / Da-Neng Wang / Etana Padan / Rajini Rao / Daxiong Fu)
- **Future Challenges**
  (*Biff Forbush* / Anjana Rao / Lukas Novotny / Andrew Ferguson)

MECHANOSENSORY TRANSDUCTION
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 22-27, 2007
PAUL BLOUNT & GLORIA MUDAY, CO-CHAIRS
ERIC HONORE, VICE CHAIR

- **An Introduction to Issues and Approaches Needed for a Comprehensive Understanding of Mechanosensing**
  (Ching Kung / Martin Chalfie / Don Ingber)
- **Genetic and Genomic Approaches to Mechanotransduction and Gravity Signaling I**
  (*Michael Gustin* / Shawn Xu / Sarah Wyatt / Elizabeth Haswell)
- **Biochemical and Biophysical Mechanisms of Mechanosensory Systems**
  (*Miriam Goodman* / Boris Martinac / Peter F. Davies / Martin Guthold)
- **Specialized Mechano- or Gravity-Sensitive Cells or Tissues**
  (*Ruth Anne Eatock* / Charles Bourque / Roger Hangarter / Ebenezer Yamoah)
- **Genetic and Genomic Approaches to Mechanotransduction and Gravity Signaling II**
  (*Patrick Masson* / Kate Beckingham / Masao Tasada)
- **Cellular and Tissue Responses to Mechanical or Gravity Stimuli**
  (John Wood / John Kiss / Jeff Holt)
- **The Role of Cytoplasmic and Extracellular Proteins in Mechanosensory Transduction**
  (*Viola Vogel* / Michael Sheetz / Benny Geiger)
- **Ionic Signaling During Mechanosensory Transduction**
  (Simon Gilroy / Helen Kennedy)
- **Hot Topics: Short Talks with Speakers Selected from the Submitted Abstracts**

MEDICINAL CHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
AUG 5-10, 2007
GEORGE HARTMAN, CHAIR
LES MCQUIRE, VICE CHAIR

- **Application of Targeted Prodrugs to Improve Pharmacokinetic and Pharmacodynamic Parameters**
  (*Manjoy C. Desai* / Dennis Smith / Richard Mackman / Mark Gallop)
- **Kinases**
  (*Mary Mader* / Michal Vieth / Mike Luzzio / Mark Fraley / Gabriel Martinez-Botella)
- **New Approaches to Cardiovascular Disease**
  (*Stephane De Lombaert* / Roger Ruggeri / Robert Stavenger)
- **Approaches Toward Treatment of Sleep and Wake Disorders**
  (*Jim Barrow* / Ling Hong Xie / Michael Letavic / Christoph Boss)
- **Disruptors of Protein-Protein Interactions**
  (*Mike Shultz*)
- **Structure-Based Drug Design**
  (*Mark Murko*)
- **Therapeutic Pain Targets**
  (*Mark Bilodeau*)
- **Late Breaking Topics**
  (*Kateri Ahrendt*)
- **Chair's Talk**
  (*Paul S. Anderson*)

MICROBIAL ADHESION & SIGNAL TRANSDUCTION
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 22-27, 2007
BONNIE BASSLER &
ARTURO ZYCHLINSKY, CO-CHAIRS
ALAIN FILLOUX &
MICHAEL STARNBACH, CO-VICE CHAIRS

- **Keynote Address 1: Bacterial Iron Wars**
  (*Michael Stambach* / Christopher T. Walsh)
- **Keynote Address 2: Host-Cell Responses to Symbiont Signals - The Molecular Dialogue of the Squid-Vibrio Partnership**
  (*Michael Stambach* / Margaret McFall-Ngai)
- **Cell to Cell Communication**
  (*Alain Filloux* / Michael Surette / Marvin Whiteley / Dale Kaiser / Roberto Kolter / Matthew Freeman)
- **Microbes and Evolution**
  (*Arturo Zychlinsky* / Joan Strassman / Manfred Milinski / Forest Rowher / Sebastian Bonhoeffer)
- **Symbiotic and Pathogenic Infections**
  (*Roberto Kolter* / Michael Starnbach / Graham Walker / Roy Gross / Brett Finlay)
- **Type III Secretion**
  (*Staffan Normark* / Guy Cornelis / Hans Wolf-Watz / Jorge Galan / Olaf Schneewind)
- **Signaling: The Host Side**
  (*Margaret McFall-Ngai* / Alan Aderem / Vishva Dixit / Michael Boutros / Emmanuelle Caron / Philippe Sansonetti)
- **Signaling: The Microbe Side**
  (*Christopher T. Walsh* / David Dubnau / Tom Silhavy / Susan Gottesman / Jean-Marc Ghigo)
- **Adhesion, Adhesins, Appendages**
  (*Brett Finlay* / Scott Hultgren / Tony Pugsley / John Telford / Alain Filloux / Staffan Normark)
- **Bacterial Cell Biology**
  (*Jorge Galan* / Zemer Gitai / Michael Laub / Piet DeBoer / Kit Pogliano)

MICROBIAL POPULATION BIOLOGY
PROCTOR ACADEMY
ANDOVER, NH
JUL 22-27, 2007
PAUL RAINEY, CHAIR
ANTONY DEAN, VICE CHAIR

- **Microbes and Ecosystem Function**
  (*Forest Rowher* / Roger Summons)
- **Evolutionary Genetics of Microbes: A Systems-Level View I**
  (*Mike Savageau* / Andreas Wagner / Lauren Ancel Myers / Uri Alon)
- **Evolutionary Genetics of Microbes: A Systems-Level View II**
  (*Roy Kishony* / Frances Arnold / Chris Voigt / Chris Knight)

- **Population Biology of Microbes**
(*Fred Cohan* / Valeria Souza / Dan Falush / Ford Doolittle / Nichole Broderick)
- **Symbiosis**
(*Greg Hurst* / Cameron Currie / Susse Kirkelund Hanson)
- **Evolution of Infectious Disease I**
(*Susanna Remold* / Troy Day / Dieter Ebert / Gary Schoolnik / Doug Berg)
- **Evolution of Infectious Disease II**
(*Richard Moxon* / Marc Lipsitch / Harmit Malik / Dan Andersson)
- **Genetics of Adaptive Evolution**
(*Paul Turner* / Rees Kassen / David D'Argenio)
- **Interesting Life History Strategies of Bacteria**
(*Francois Taddei* / Richard Losick / Jack Werren)

MICROFLUIDICS, PHYSICS & CHEMISTRY OF
WATERVILLE VALLEY RESORT
WATERVILLE VALLEY, NH
JUL 15-20, 2007
SABETH VERPOORTE, CHAIR
AMY HERR &
JUAN SANTIAGO, CO-VICE CHAIRS

- **Keynote Lecture: Microfluidics and MEMS for Biomolecular Analysis**
(Hiroyuki Fujita)
- **Short Presentations: Student Posters**
(*Sander Koster*)
- **Flow Imaging and Diagnostics**
(*Jaap den Toonder* / Jerry Westerweel / John G. Georgiadis)
- **Handling (Bio)particles in Microfluidic Systems**
(*James Landers* / Klavs Jensen / Joel Voldman)
- **Electrokinetic Phenomena at the Nanometer Scale**
(*Juan Santiago* / Ulrich Tallarek / Martin Bazant)
- **Nano(bio)technology: Chemical and Biochemical Locomotion**
(*Armand Ajdari* / Ayusman Sen)
- **Novel Analysis and Detection Strategies**
(*Susan Lunte* / Brian MacCraith / Norman Dovichi)
- **Functional Materials**
(*Yoshinobu Baba* / Jörg Kutter)
- **Working with Cells in Microfluidic Devices**
(*Shuichi Takayama* / Teruo Fujii / Mehmet Toner)
- **Future Funding and Markets for Micro- and Nanofluidics**
(*Laurie Locascio* / Jeff Fortin / Dennis Polla)

MOLECULAR & CELLULAR BIOENERGETICS
PROCTOR ACADEMY
ANDOVER, NH
JUN 17-22, 2007
FEVZI DALDAL, CHAIR
DAVID NICHOLLS, VICE CHAIR

- **Electron Transfer, Proton Transfer, Role of Water in Proteins**
(Marilyn Gunner / P. Leslie Dutton / Judith P. Klinman / David Beratan)
- **Maturation and Assembly of Multi-subunit, Multi-cofactor Membrane Proteins**
(Sabeeha Merchant / Michael K. Johnson / Stuart J. Ferguson / H-Georg Koch)
- **F0-F1 ATP Synthase: Structure-Function and Assembly**
(Wolfgang Junge / John E. Walker / Stanley D. Dunn)
- **Complex I and Complex III: Structure-Function and Biogenesis**
(Tomoko Ohnishi / William A. Cramer / Leo Sazanov / Akhil Vaidha)
- **Mitochondrial Links to Apoptosis, Cancer, Aging and Therapeutics**
(Takao Yagi / Craig B. Thomson / Paul M. Hwang / Lenny Guarente)
- **Molecular and Cellular Bioenergetics Workshops**
(Anthony R. Crofts / Bianca Barquera / Stephan Wilkens / Shelagh Ferguson-Miller)
- **V-ATPase Structure-Function and Cell Biology**
(Patricia Kane / Michael Forgac / Michael Levin)
- **Complex II and Complex IV: Structure-Function and Biogenesis**
(Hartmut Michel / Robert B. Gennis / Garry Cecchini / Marten Wikstrom / Jon Hosler / Maik Huttemann)
- **From Omics and Imaging to Bio-nano Frontiers**
(A tribute to Britton Chance)

MOLECULAR MEMBRANE BIOLOGY
PROCTOR ACADEMY
ANDOVER, NH
JUL 8-13, 2007
BENJAMIN GLICK, CHAIR
SEAN MUNRO, VICE CHAIR

- **Membrane Domains**
(*Scott Emr* / Bill Wickner / David Stephens / Suzanne Pfeffer)
- **Membrane Fusion**
(*Hugh Pelham* / Josep Rizo / James McNew / Reinhard Jahn / Andreas Mayer)
- **Lipid Transport and Localization**
(*Fred Maxfield* / Dawn Brasaemle / Will Prinz / Peter Espenshade)
- **Organelle Structure and Dynamics**
(*Lois Weisman* / Janet Shaw / Liza Pon / Chris Kaiser / Catherine Rabouille)
- **Pathogens and Membrane Traffic**
(*Pascale Cossart* / Norma Andrews / Craig Roy / Tom Wileman)
- **Vesicle Formation**
(*Sandy Schmid* / Pietro De Camilli / Anne Spang / Bill Balch / Randy Schekman / Charlie Barlowe)
- **Reaching the Plasma Membrane**
(*Peter Novick* / Vivek Malhotra / Patrick Brennwald / Ira Mellman)
- **Traversing the Golgi**
(*Alberto Luini* / Adam Linstedt / Francis Barr / Jim Rothman / Aki Nakano)
- **Entering the ER**
(*Ari Helenius* / Tom Rapoport / Gunnar von Heijne / Peter Walter)

MOLECULAR THERAPEUTICS OF CANCER
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 22-27, 2007
PHILLIP DENNIS, CHAIR
JAMES WINKLER, VICE CHAIR

- **MicroRNA**
(*Carlo Croce* / Carlo Croce / Curtis Harris / Paul Foster)
- **Autophagy, the Unfolded Protein Response and Cancer**
(*Linda Hendershot* / Linda Hendershot)
- **Akt and mTOR**
(*Mary Ann Bjornsti* / Nissim Hay / David Sabatini)
- **Stem Cells in Epithelial Cancers**
(*Max Wicha* / Max Wicha / Sam Jones / Thomas Look)
- **Emerging Kinase Targets**
(*Robert Kramer* / Ravi Salgia / Moitreyee Kishore)
- **Repositioning Old Drugs as Cancer Therapeutics**
(*Patricia Steeg* / Patricia Steeg / Warren Chow / Ping Dou)
- **Making the Untreatable Treatable: Lessons from Kidney Cancer**
(*Ronald Bukowski* / Ronald Bukowski / Marston Linehan)
- **Exosomes, Tetraspannins, and Lipidomics**
(*Alain Delcayre* / Alain Delcayre / Martin Hemler / Alex Brown)
- **What Have We Learned from Targeting VEGF?**
(*Hiliary Calvert* / Alan Sandler / Afshin Dowlati)

MOLYBDENUM & TUNGSTEN ENZYMES
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 1-6, 2007
CAROLINE KISKER &
ALASTAIR MCEWAN, CO-CHAIRS
MARTIN KIRK &
MARIA JOAO ROMAO, CO-VICE CHAIRS

- **Keynote Talk 1: Molybdenum Cofactor Synthesis and Beyond**
(Ralf Mendel)
- **Keynote Talk 2: Tribute to Edward Stiefel**
(Sharon Burgmayer)
- **Sulfite Oxidase Family**
(*K.V. Rajagopalan* / Ulrike Kappler / Joel Weiner / Heather Wilson / John Enemark)
- **Xanthine Oxidase Family**
(*Takeshi Nishino* / Ortwin Meyer / Wilfred R. Hagen / Ken Okamoto / Charles Young)
- **DMSO Reductase Family**
(*Graham George* / Johann Heider / Clive S. Butler / Oliver Einsle / Julea N. Butt)
- **Molecular and Cellular Biology of Mo and W**
(*Maria Joao Romao* / Axel Magalon / Frank Sargent)
- **Mo Cofactor and Beyond**
(*Silke Leimkühler* / Andrew T. Smith / Florian Bittner / Günter Schwarz / Sharon Burgmeyer / C. David Garner)
- **Environmental Aspects**
(*Joanne M. Santini* / Jeffrey A. Gralnick / Chad W. Saltikov / Anne-K. Duhme-Klair / David J. Richardson)
- **Mechanisms of Catalysis and Electron Transfer**
(*Martin L. Kirk* / Paul V. Bernhardt / Russ Hille / Matthias Hofmann / Christian J. Doonan)
- **Keynote Talk 3: Moving Electrons and Protons together, With and Without Metals - Thermodynamics and Kinetics**
(Jim Mayer)

MOTILE & CONTRACTILE SYSTEMS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 8-13, 2007
MARGARET A. TITUS, CHAIR
KERRY BLOOM, VICE CHAIR

- **Keynote Talk: Mitotic Spindle Morphogenesis in Chromosome Segregation and Beyond**
  (Yixian Zheng)
- **Molecular Mechanisms of Motor Proteins**
  (*Susan Gilbert* / Enrique De La Cruz / David Warshaw)
- **Cytoskeletal Polymer Dynamics**
  (*Dyche Mullins*)
- **Spindle Assembly**
  (*Alexey Khodjakov*)
- **Movement in a Three-Dimensional Environment**
  (*Denise Montell* / John Condeelis)
- **Intracellular Transport**
  (*Kristen Verhey* / Volodya Gelfand)
- **Kinetochores and Chromosome Movements**
  (*Ted Salmon* / Trisha Davis / David Sharp)
- **Cytokinesis**
  (*Karen Oegema* / Tom Pollard)
- **Cell Polarity and Signalling**
  (*Tony Bretscher* / James Nelson)

MYCOTOXINS & PHYCOTOXINS
COLBY COLLEGE
WATERVILLE, ME
JUN 17-22, 2007
KELLY REIN & KENNETH VOSS, CO-CHAIRS
BARBARA BLACKWELL &
ROBERT DICKEY, CO-VICE CHAIRS

- **Human Exposures**
  (Paul Alan Cox / George Bailey / Wayne W. Carmichael)
- **Public Health and Epidemiology**
  (*Lorraine C. Backer* / Chris Wild / Gordon Shephard / George Luber / Pauline Jolly / Lora E. Fleming)
- **Detection Technologies for Organisms and Toxins**
  (*Robert Dickey* / Michael Appell / Kristian Nielsen)
- **New Toxins, Metabolites and Synthesis**
  (*Robert Gawley* / Craig Forsyth / Manfred Metzler / Timothy F. Jamison / Michael A. Quilliam)
- **Molecular Genetics of Toxin Biosynthesis**
  (*Cindy Heil* / Fran Van Dolah / William Nierman / Jun'ich Kobayashi)
- **Toxin Biosynthesis, Regulation and Function**
  (*Jujiang Yu* / Brett A. Neilan / Franz Berthiller / Douglas L. Crawford / Mark Wells / Bruce Campbell)
- **Toxicogenomics and Molecular Mechanisms**
  (*Wayne Bryden* / Janee Gelineau-van Waes / Kathi Lefebvre / James Pestka)
- **Molecular Mechanisms II**
  (*Robert McPhail* / Alice Hudder / Angela Mally / Gerhard Adam / Allen R. Place)
- **Mediators of Pathogenesis**
  (Michael Kolomiets / Tony Glenn)
- **Economic Impacts**
  (*Mary Trucksess* / Felicia Wu)

NATURAL PRODUCTS
TILTON SCHOOL
TILTON, NH
JUL 22-27, 2007
DAVID UEHLING, CHAIR
SCOTT GILBERTSON, VICE CHAIR

- **Total Synthesis of Natural Products**
  (Phil Baran / Stephen Martin / Richard Taylor)
- **Advances in Natural Products Synthesis and Isolation**
  (William Fenical / Jay Keasling / John Wood)
- **Natural Products Synthesis and Methodology**
  (Justin DuBois / Toru Fukuyama / Peter Jacobi / Mark Lautens)
- **Catalytic Synthetic Methodology I**
  (Robert Grubbs / Richard Larock)
- **Catalytic Synthetic Methodology II**
  (Greg Fu / Eric Jacobsen / Andreas Pfaltz)
- **New Methods in Synthesis of Natural Products**
  (Janine Cossy / Richmond Sarpong / Jan Van Maarseveen)
- **Chemical Communication**
  (Helen Blackwell / Julia Kubanek / Walter Leal)
- **Chemical Biology**
  (David Liu / Anna Mapp / Raj Singh)
- **Medicinal and Bioorganic Chemistry**
  (Michael Luzzio / Sergey Kozmin / Marvin Miller / Emma Parmee)
- **Medicinal and Process Chemistry**
  (Mui Cheung / Steve Davidsen / Eric Moher)

NEURAL CIRCUITS & PLASTICITY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 1-6, 2007
RAFAEL YUSTE, CHAIR
TAKAO HENSCH, VICE CHAIR

- **Keynote Talk 1: TBA**
  (Richard Axel)
- **Chemical Senses**
  (*Gilles Laurent* / Cori Bargman / Catherine Du Lac)
- **Retina**
  (*Marcus Meister* / Rachel Wong / Marla Feller)
- **Hippocampus**
  (*Erin Schuman* / May-Britt Moser / Matthew Wilson)
- **Hot Topics: Neurogenesis/Stem Cells**
  (*Fernando Nottebohm* / Pierre-Marie Lledo / Fred Gage)
- **Neocortex**
  (*Clay Reid* / Hannah Monyer / Ed Callaway)
- **Keynote Talk 2: TBA**
  (Susumu Tonegawa)
- **Animal Cognition**
  (*Anne Graybiel* / Dan Margoliash / Marc Hauser)
- **Human Cognition**
  (*Joy Hirsch* / Nancy Kanwisher / Read Montague)
- **Hot Topics: New Methods**
  (*Winfried Denk* / Gero Miesenboeck / Julie Simpson)

NEUROTROPHIC FACTORS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 17-22, 2007
DAVID GINTY, CHAIR
WILLIAM MOBLEY, VICE CHAIR

- **Trophic Factor Signaling I**
  (*Luis Parada* / Barbara Hempstead / Gary Landreth / Gail Mandel)
- **Trophic Factors, Plasticity and Behavior**
  (*Moses Chao* / Rene Hen / Lisa Monteggia / Lino Tessarollo / Martha Constantine-Paton)
- **Neuronal Growth Factors and Development I**
  (*Bill Snider* / Rudiger Klein / Gabriel Corfas / Sam Pfaff)
- **Trophic Factors and Neural Disease**
  (*Louis Reichardt* / Frank Longo / Eva Feldman / Ray Bartus / Larry Benowitz / Jeff Kordower)
- **Tropic Factor Signaling II**
  (*Carlos Ibanez* / Francis Lee / Enrico Tongiorgi / David Kaplan / Bruce Carter)
- **Tropic Factor and Plasticity**
  (Mike Ehlers / Mu-ming Poo / Kelsey Martin / Nancy Ip)
- **Trophic Factors and Developmental Disorders**
  (*Rosalind Segal* / Erika Holzbaur / Jack Griffin / David Katz / Yanmin Yang)
- **Neuronal Growth Factors and Development II**
  (*Story Landis* / Tony Pawson / Tom Jessell / Silvia Arber / Dennis O'Leary)
- **Trophic Factors and Synaptic Functions**
  (*Yves Alain Barde* / Andres Buonanno / Patricia Salinas / Shumin Duan)

NONLINEAR SCIENCE
COLBY COLLEGE
WATERVILLE, ME
JUN 24-29, 2007
ANNA LIN, CHAIR
ROBERT BEHRINGER, VICE CHAIR

- **Glassy, Disordered and Granular Systems I**
  (Wim van Saarloos / Hernan Maske / Mark Shattuck)
- **Pattern Formation I**
  (Gunter Ahlers / Ehud Meron / Irving Epstein)
- **Dynamic Networks**
  (Steve Potter / Bill Ditto / Bruce Gluckman)
- **Fracture**
  (Jay Fineberg / Steve Morris)
- **Glassy, Disordered and Granular Systems II**
  (Bulbul Chakraborty / Eric Weeks / L. Mahadevan)
- **Biological Systems**
  (Peter Jung / Kyoung Lee / Oscar Mesquita)
- **Instabilities**
  (Mogens Levinsen / Ed Ott / Dan Lathrop / Linda Smolka)
- **Network Dynamics**
  (Nishikawa Takashi)
- **Pattern Formation II**
  (Oliver Steinbock)

Celebrating our 75th Anniversary on the Frontiers of Science (1931-2006)

NUCLEAR CHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 3-8, 2007
AUGUSTO MACCHIAVELLI, CHAIR
BETTY TSANG, VICE CHAIR

- **New Developments in Nuclear Structure Theory**
  (J. Dudek / S. Frauendorf / A. Schwenk / R. Wyss)
- **The Structure of Light Nuclei**
  (A. Wuosmaa / A. Schiller)
- **Nuclear Structure Far From Stability: Proton-Rich Nuclei**
  (P. Butler / A. Goergen / S. Lenzi / K. Rykaczewski / D. Sarantites / D. Seweryniak)
- **Neutron-Rich Nuclei**
  (R. Janssens / K. Jones / P. Mantica / K. Starosta / A. Stuchbery)
- **Highlights from New Facilities**
  (J. Gerl / C. Svensson)
- **Phenomena at High-Spins**
  (C. Beausang / H. Hubel / M. Riley)
- **Aspects of Pairing in Nuclei**
  (R.M. Clark / P. van Isacker)
- **Properties of Warm Nuclei**
  (Th. Dossing / A. Lopez Martin / D. Savran / F.S. Stephens)
- **Nuclear Structure and Isomeric States**
  (G. Lane / P. Regan)
- **Properties of Heavy Nuclei**
  (A. Afanasjev / T.L. Khoo)
- **Nuclear Astrophysics**
  (A. Champagne)
- **Double Beta Decay**
  (E. Norman)
- **New Instruments and Applications**
  (I.Y. Lee / J. Simpson / L. Bernstein)

NUCLEAR PHYSICS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 15-20, 2007
MICHAEL RAMSEY-MUSOLF, CHAIR
STEVE VIGDOR, VICE CHAIR

- **The Nuclear Physics of Stars**
  (Sanjay Reddy / Gail McLaughlin / Yong Qian / Michael Weischer)
- **Neutrinos in Nuclear Physics**
  (*Baha Balantekin* / Robert McKeown / Hamish Robertson / Nicole Bell / Steve Elliott / Bonnie Fleming / John Beacom)
- **Challenges in Nuclear Structure**
  (*Witek Nazarewic* / Rocco Schiavilla / David Dean / Don Geesaman)
- **QCD and the Structure of Hadrons**
  (*Jian-ping Chen* / Xiangdong Ji / Richard Milner / Kostas Orginos / Michel Garcon / Zein-Eddine Meziani / Nilanga Liyanage)
- **Quarks, Gluons, and Spin**
  (*Ulrich Heinz* / Bill Zajc / Raju Venugopolan / Naomi Makins)
- **CP-Violation and the Origin of Matter**
  (*Susan Gardner* / Steve Lamoreaux / Zheng-Tian Lu / Chen-Yu Lu / Maxim Pospelov / Vincenzo Cirigliano / Stefano Profumo)
- **QCD and Effective Field Theorys**
  (*Roxanne Springer* / Iain Stewart / Henry Weller / Elizabeth Jenkins / Daniel Philips)
- **Symmetry Tests in Nuclear Physics**
  (*Geoff Greene* / Barry Holstein / Shelley Page / Krishna Kumar / Bill Marciano / Tim Chupp / Dave Hertzog)
- **New Horizons**
  (*Krishna Rajagopal* / David Kaplan / Gordon Cates)

NUCLEIC ACIDS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 3-8, 2007
CYNTHIA BURROWS &
JOSEPH (JODY) PUGLISI, CO-CHAIRS
JAMIE CATE &
PAUL MODRICH, CO-VICE CHAIRS

- **Keynote Lectures: Frontiers of DNA & RNA Research**
  (*C. Burrows* / *J. Puglisi* / Jacqueline Barton / Ignacio Tinoco)
- **Molecular Recognition and Processing of DNA Damage**
  (*Susan Wallace* / Jim Stivers / Orlando Shärer / Tom Kunkel / Steve West)
- **Nucleosomes and DNA Dynamics**
  (*Karolin Luger* / Jon Widom / Geeta Narlikar / Steve Kowalczykowski)
- **Ribozymes & Riboswitches: Structural Basis for Function**
  (*Adrian Ferre-d'Amare* / David Lilley / Martha Fedor / Dan Hershlag / Scott Strobel)
- **RNA Interference: Pathways to Gene Function**
  (*Lemor Joshua-Tor* / Dinshaw Patel / Peter Sarnow)
- **Transcription Initiation and Regulation**
  (*Anna Mapp* / Tom Kodadek / Richard Ebright / Patrick Cramer)
- **RNA Splicing Mechanisms**
  (*Reinhard Luhrmann* / Christine Guthrie / Kristen Lynch)
- **The Ribosome**
  (*Jamie Cate* / Venki Ramakrishnan / James Williamson / Jennifer Doudna / Wolfgang Wintermeyer)
- **Emerging Technologies: Synthetic Biology**
  (*Floyd Romesberg* / Christina Smolke / Andreas Marx / Milan Stojanovic)

NUCLEOSIDES, NUCLEOTIDES & OLIGONUCLEOTIDES
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 1-6, 2007
JYOTI CHATTOPADHYAYA, CHAIR
VARSHA GANDHI, VICE CHAIR

- **Novel Mechanism-Based Inactivators**
  (JoAnne Stubbe / Tomas Cihlar / David B. Olsen)
- **DNA/RNA Chemistry**
  (Kevin Weeks / Marv Caruthers / Zhen Xi)
- **RNA Targeting & Delivery**
  (Mano Manoharan / Alan Gewirtz / Sudhir Agarwal)
- **Conformationally-Constrained Nucleosides**
  (Jesper Wengel / Riad Agbaria)
- **DNA Repair**
  (Jacqueline Barton / Thomas Carell)
- **DNA/RNA Interactions**
  (Erik Kool / Piet Herdiwijn)
- **Functional Oligos**
  (Naoki Sugimoto / Chad Mirkin)

OCULOMOTOR SYSTEM BIOLOGY
BATES COLLEGE
LEWISTON, ME
JUL 8-13, 2007
NEERAJ GANDHI &
JENNIFER GROH, CO-CHAIRS
KATHLEEN CULLEN &
PAUL MAY, CO-VICE CHAIRS

- **Keynote Talk 1: The Eyes Have It - Action Chunking and Oculomotor Control**
  (Ann Graybiel)
- **Keynote Talk 2: The Primate Oculomotor System - A Window Onto Value-Based Decision Making**
  (William Newsome)
- **Action in the Oculomotor Periphery**
  (*Paul May* / Francisco Andrade / Roland Blumer / Michael Goldberg / Angel Pastor)
- **Eye-Head Coordination**
  (*Laurent Goffart* / Kikuro Fukushima / Daniel Guitton / Paul May / David Waitzman)
- **Motor Preparation**
  (*Neeraj Gandhi* / Brian Corneil / Jacqueline Gottlieb / Tirin Moore / Kirk Thompson)
- **Neuroethology - The Impact of Nature's Experiments on Oculomotor Systems**
  (*Robert Baker* / Herwig Baier / David Dickman / Harvey Karten / Susan Udin)
- **Predictive Eye Movements**
  (*Douglas Munoz* / Graham Barnes / Stephen Heinen / Gillian O'Driscoll / Mark Shelhamer)
- **Vestibular System Dynamics: From Cells to Circuits**
  (*Kathleen Cullen* / Gay Holstein / Robert McCrea / Jennifer Raymond / Pierre-Paul Vidal)
- **Visuospatial Processing for Eye Movements**
  (*Michael Goldberg* / Vivien Casagrande / Douglas Munoz / Marc Sommer / Robert Wurtz)
- **Hot Topics**
  (*Jennifer Groh* / Speakers to be determined from abstract submissions)

ORGANIC REACTIONS & PROCESSES
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 15-20, 2007
JOS BRANDS, CHAIR
GREGORY COOK, VICE CHAIR

- **Organometallics in Synthesis I**
  (*Christina White* / Alexandre Alexakis / Richmond Sarpong)
- **New Synthetic Methodology and Process Research I**
  (*Ioannis Houpis* / Jennifer Albaneze-Walker / Rudy Broeck / Scott Nelson / Samir Zard)
- **Asymmetric Catalysis I**
  (*Jeffrey Bode* / Matthias Beller / Eric Jacobsen / Keji Maruoka)
- **Molecular Machines and Receptors**
  (*Jinquan Yu* / Eric Anslyn / Ben Feringa / David Leigh)
- **Organometallics in Synthesis II**
  (*Jerry Murry* / Amir Hoveyda / Jennifer Love)
- **New Synthetic Methodology and Process Research II**
  (*Michel Coutourier* / Stephen Challenger / Martin Karpf / Jim Leighton / Dietrich Steinhuebel)

- **Asymmetric Catalysis II**
(*Sheryl Wiskur* / Erick Carreira / Jeffrey Johnson / Matthew Gaunt / Benoit Pugin)
- **Natural Product Synthesis**
(*Elizabeth Jarvo* / Timothy Jamison / Joseph Ready / John Wood)

ORGANOMETALLIC CHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 8-13, 2007
NORA RADU, CHAIR
ALAN GOLDMAN, VICE CHAIR

- **Kickoff Session: A Bipartisan Approach to Organometallic Chemistry**
(*Alan Goldman* / Michael Heinekey / James Boncella)
- **New Ligand Platforms**
(*Richard Broene* / John Arnold / Philip Mountford / Warren Piers / Yutaka Matsuo)
- **New Reactivity and Transformations: s & p Block Chemistry**
(*Soley Kristjansdottir* / Christopher Reed / Carl Busacca / David Glueck)
- **Asymmetric Catalysis**
(*Alan Allgeier* / Bernadette Donovan-Merkert / Amir Hoveyda / Patrick Walsh)
- **Mechanistic and Theoretical**
(*Richard Fisher* / Arkadi Vigalok / Marc Johnson / Odile Eisenstein)
- **New Reactivity and Transformations: d Block Chemistry**
(*Gary Casty* / Kristopher McNeill / Alan Heyduk / Mikhail Barybin)
- **Organometallics in Materials Chemistry**
(*Don Tilley* / Christina Older / Keith Hall / Jillian Buriak)
- **Applications in Organic Methodology and Pharmaceuticals**
(*Mitch Smith* / Alison Frontier / Anil Guram / Peter Sadler)
- **Back to the Future**
(*Tom Baker* / Gerard Parkin / Dan Nocera)

GRADUATE RESEARCH SEMINAR: ORGANOMETALLIC CHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 6-8, 2007
ELIZABETH MADER & NORA RADU, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Organometallic Chemistry** is a three-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Organometallic Chemistry** Gordon Research Conference will take place at the same location, immediately following the Seminar.

- **Frontiers in Organometallic Chemistry**
(*Bernadette Donovan-Merkert* / Christopher Cummins / Emilio Bunel)
- **Organometallics in Organic Chemistry**
(*Robert Bergman*)
- **Organometallics in Materials Chemistry and Biology**
(*Dan Vanderlende*)
- **Physical and Computational Methods**
(*Jennifer Love*)
- **Round Table Discussion: Career Opportunities for Organometallic Chemists**
(*Elizabeth Mader* / Anthony England / Susan Kegley / Nora Radu)

ORIGINS OF SOLAR SYSTEMS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 8-13, 2007
LEE HARTMANN, CHAIR
SARA RUSSELL, VICE CHAIR

- **Results from Stardust and Dust in Protoplanetary Disks**
(*Scott Sandford* / Mike Zolensky / Dan Watson)
- **Radioisotopes and Solar System Chronology**
(*Andy Davis* / Martin Bizzarro / Marianna Cosarinsky / Ed Young)
- **Irradiation Within the Solar System**
(*Frank Podosek* / Mini Wadhwa / Matthieu Gounelle)
- **Evolution and Structure of Protoplanetary Disks**
(*Suzan Edwards* / Lynne Hillenbrand / Elise Furlan / Sean Andrews)
- **Debris Disks**
(*Scott Kenyon* / Michael Meyer / Amaya Moro-Martin)
- **Disk Physics and Planet Formation**
(*Doug Lin* / Charles Gammie / Ken Rice / Zoe Leinhardt)
- **Exoplanets**
(*Alan Boss* / David Bennett / Sara Seager)
- **Chemistry in Protoplanetary Disks and the Solar Nebula**
(*Ted Bergin* / Yuri Aikawa / Jim Lyons)
- **Chondrule Formation**
(*Rhian Jones* / Harold Connolly / Fred Ciesla)

PHAGOCYTES
BRYANT UNIVERSITY
SMITHFIELD, RI
JUN 10-15, 2007
JOEL SWANSON, CHAIR
LINDA MCPHAIL, VICE CHAIR

- **Keynote Lecture: Dynamics of NADPH Oxidase Assembly**
(Mary Dinauer)
- **Phagocyte Dynamics *In Vivo***
(*John Curnutte* / Jonathan Mathias / Mark Miller)
- **Chemotaxis**
(*Phil Murphy* / Peter Devreotes / Diane Cox / Andrew Luster)
- **Development and Differentiation**
(*Michael Hengartner* / Alberto Mantovani / Richard Lang / Jay Kolls)
- **Phagocytosis**
(*Eric Brown* / Clifford Lowell / Emmanuelle Caron / Sergio Grinstein / Lynda Stuart)
- **Organelle Trafficking**
(*David Russell* / Norma Andrews / Mark Marsh / Gisou van der Goot)
- **Microbicidal Chemistries**
(*William Nauseef* / Deborah Nelson / Gary Bokoch / Tony Kettle / Gregory Taylor)
- **Innate and Specific Immunity**
(*Alan Ezekowitz* / Ira Mellman / Daniel Portnoy / Ruslan Medzhitov)
- **Inflammation**
(*Ulla Knaus* / Robert Kastelein / Denise Monack / Kate Fitzgerald / Masanori Aikawa)
- **Atherosclerosis**
(*Samuel Silverstein* / Stanley Hazen / Tracie Seigol / Samuel Wright)

PHOSPHORYLATION & G-PROTEIN MEDIATED SIGNALING NETWORKS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 10-15, 2007
HENRIK DOHLMAN &
JOANN TREJO, CO-CHAIRS
J. SILVIO GUTKIND &
JEAN WANG, CO-VICE CHAIRS

- **Keynote Talk: Chemotactic Signaling**
(Peter Devreotes)
- **Opening Session: Systems-Level Analysis of Signaling**
(Rama Ranganathan / Alex Brown / Bryan Roth)
- **G Protein Coupled Receptors**
(*Mark Von Zastrow* / Graeme Milligan / Adriano Marchese / Nevin Lambert)
- **Non-Receptor Exchange Factors**
(*David Siderovski* / Xavier Morin / Fengwei Yu / Kenneth Miller)
- **G Proteins**
(*Heidi Hamm* / John Sondek / Catherine Berlot / Alan Smrcka)
- **RGS Proteins**
(*Kendall Blumer* / Rick Neubig / Peter Chidiac / John Hepler / Marie Burns)
- **G Protein Modifications**
(*Maurine Linder* / Anne Kenworthy / Robert Deschenes / Mark Philips)
- **Effectors Linked to Small G Proteins**
(*Silvio Gutkind* / Ken Harden / Wei-Jen Tang / Jean Wang)
- **Effectors and Signaling Networks**
(*Pat Casey* / Michael Koelle / Fuyu Tamanoi)

PHOTOCHEMISTRY
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 8-13, 2007
LINDA JOHNSTON, CHAIR
BRUCE ARMITAGE &
MICHAEL WASIELEWSKI, CO-VICE CHAIRS

- **Fluorescence Based Biosensors**
(Nancy Greenbaum / Alan Waggoner)
- **Materials**
(Rene Janssen / Gerald Meyer / Kirk Schanze)
- **Mechanistic Organic Photochemistry**
(Neil Branda / Richard Givens / John Toscano)
- **Photochemistry on the Nanoscale**
(Moungi Bawendi / Daniel Falvey)
- **Photoinduced Electron Transfer in Biomolecules**
(Tetsuro Majima / Ana Moore)
- **Single Molecule Spectroscopy**
(Sunney Xie)
- **Supramolecular Photochemistry**
(Cornelia Bohne / Jochen Mattay / V. Ramamurthy)
- **Ultrafast Dynamics**
(Todd Martinez / Erik Nibbering / Albert Stolow)

PHYSICAL ORGANIC CHEMISTRY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUN 24-29, 2007
R. STANLEY BROWN, CHAIR
PETER SCHREINER, VICE CHAIR

- **Nanochemistry and Things That Move** (*Chris Easton* / Ben Feringa / Tito Scaiano / Glen Miller)
- **Carbenes and Reactive Intermediates** (*Daniel O'Leary* / Dina Merrer / Willie Leigh / Holger Bettinger / James Jackson)
- **Computational Chemistry and Applications** (*Tania Cordova* / Amnon Stanger / Shmaryahu Hoz / Uta Wille)
- **Mechanistic Considerations in Synthesis** (*Kathleen Kilway* / Cathleen Crudden / Marisa Koslowski / Douglas Klump / Carol Parish)
- **Fullerenes / Aromatics** (*Edward Clennan* / Cheryl Stevenson / Luis Echegoyan / Graham Bodwell)
- **Enzyme Mechanisms and Mimics** (*John P. Richard* / Jeffrey Keillor / Andrew Bennet / Nick Williams / Anatoli Yatsimirski)
- **Gas Phase Reactions** (*Richard Nagorski* / Jeehiun Lee / Veronica Bierbaum)
- **Eclectic Organic Chemistry / Catalysis and Concepts** (*Robin Hicks* / John Baldwin / Tyler McQuade / Bart Kahr / Colin Nuckolls)
- **Poster Session Talks** (*Peter R. Schreiner* / Speakers to be determined from posters at Conference)

PLANT METABOLIC ENGINEERING
TILTON SCHOOL
TILTON, NH
JUL 15-20, 2007
ERICH GROTEWOLD, CHAIR
JOE CHAPPELL, VICE CHAIR

- **Metabolic Networks and Engineering: Before Plants** (*Reinhardt A. Rosson* / Claudia Schmidt-Dannert / Christina D. Smolke)
- **Organization and Evolution of Plant Metabolic Pathways** (*Thomas Mitchell-Olds* / Wolf B. Frommer / Mary Schuler / Thomas Vogt)
- **Enzyme Plasticity: Friend or Foe in Metabolic Engineering?** (*Anne Osbourn* / Reuben Peters / Birger L. Møller / Natalia Dudareva)
- **Regulatory Factors for Metabolic Engineering** (*Neal Gutterson* / Kazuki Saito / Bert van de Zaal / Masaru Takagi)
- **Transport and Sequestration of Plant Chemicals** (*Natasha Raikhel* / Philip Rea / Christoph Benning)
- **Harvesting Energy and Bioconversion** (*Sharlene Weatherwax* / Don Ort / Alison Smith / Bärbel Hahn-Hägerdal)
- **Engineering Complex Agronomic Traits** (*Andrew Hanson* / Doug Cook / Françoise Vedele)
- **Plant Metabolic Engineering for the Developing World** (*Maarten J. Chrispeels* / Mary Lou Guerinot / Glaucia Souza / Víctor Loyola-Vargas / Richard Sayre)
- **Window to the Future** (*Dirk Inze* / Jian-Kang Zhu / Mike Tyers)

GRADUATE RESEARCH SEMINAR: PLANT METABOLIC ENGINEERING
TILTON SCHOOL
TILTON, NH
JUL 13-15, 2007
JOE CHAPPELL, ERICH GROTEWOLD &
ELEANORE WURTZEL, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Plant Metabolic Engineering** is a two-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Plant Metabolic Engineering** Gordon Research Conference will take place at the same location, immediately following the Seminar.

POLYAMINES
WATERVILLE VALLEY RESORT
WATERVILLE VALLEY, NH
JUN 17-22, 2007
LEENA ALHONEN &
MARGARET PHILLIPS, CO-CHAIRS
SENYA MATSUFUJI &
PATRICK WOSTER, CO-VICE CHAIRS

- **Diversity of Polyamine Function** (*Phil Coffino* / Alan Fairlamb / Kazuei Igarashi)
- **Biosynthetic Pathways and Transport** (*Patrick Woster* / *Senya Matsufuji* / Miguel Angel Medina / Ted Sybertz / Sigrid Roberts / Otto Phanstiel IV)
- **Catabolic Pathways** (*Bob Casero* / Steve Ealick / Kami Kim / Maria Bewley)
- **Systems Biology** (*Keiko Kashiwagi* / Oliver Fiehn / Tony Michael / Benjamin Tu / Dave Morris)
- **Post-Translational Regulation** (*Myung Park* / John Atkins / Ursula Mangold / Kuang Yu Chen)
- **Signalling** (*Stina Ordesson* / Susan Gilmour / Lisa Shantz / Keith Wilson / Tomonobu Kusano)
- **Bacterial Pathogenesis** (*Anthony Pegg* / Paul Williams / Phil Rather / Matt Mulvey)
- **Mammalian Pathogenesis** (*Gene Gerner* / Erkki Holttä / Carl Porter / Juhani Jänne / Laurence Marton)
- **Keynote: Clinical Applications** (*Nigel Yarlett* / Cy Bacchi)

GRADUATE RESEARCH SEMINAR: POLYAMINES
WATERVILLE VALLEY RESORT
WATERVILLE VALLEY, NH
JUN 15-17, 2007
MARC CERRADA-GIMENEZ, COLIN HANFREY,
MARGARET PHILLIPS &
ERIN WILLERT, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Polyamines** is a three-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Polyamines** Gordon Research Conference will take place at the same location, immediately following the Seminar.

POLYMER COLLOIDS
TILTON SCHOOL
TILTON, NH
JUN 24-29, 2007
ALEX VAN HERK, CHAIR
WOLF-DIETER HERGETH, VICE CHAIR

- **Controlled Radical Polymerization / Metal Catalyzed Polymerization Applied in Heterogeneous Systems** (*Bernadette Charleux* / Patrick Lacroix-Desmazes / Jerome Claverie)
- **Fundamentals in Emulsion Polymerization** (*Pete Lovell* / Rajan Venkatesh / Bob Gilbert / Klaus Tauer)
- **Deliberate and Unwanted (Hetero)coagulation** (*Tim McKenna*)
- **Colloidal Interactions** (*David Weitz* / Jan Spitzer / Martien Cohen Stuart)
- **Colloidal Microgels** (Todd Hoare / Kazunari Akiyoshi)
- **Polymeric-Inorganic Nanocomposites** (*Elodie Bourgeat-Lami* / Stefan Bon / Katharina Landfester / Brian Hawkett)
- **Morphology of Latex Particles** (Masayoshi Okubo / Don Sundberg)
- **Special Topics in Emulsion Polymerization** (Axel Müller / Leon Bremer)
- **High Throughput Techniques in Emulsion Polymerization** (Radislav Potyrailo)

GRADUATE RESEARCH SEMINAR: POLYMER COLLOIDS
PROCTOR ACADEMY
ANDOVER, NH
JUN 22-24, 2007
WOLF-DIETER HERGETH, NIELS SMEETS,
FATIMA TORRES &
ALEX VAN HERK, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Polymer Colloids** is a three-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Polymer Colloids** Gordon Research Conference will take place at Tilton School in Tilton, NH, immediately following the Seminar.

POLYMERS (EAST)
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 17-22, 2007
KAREN WOOLEY, CHAIR
TIMOTHY LONG, VICE CHAIR

- **Switching Systems** (*Douglas J. Kiserow* / Timothy M. Swager / Takashi Kato)
- **Advanced Catalysis** (*Eric Fossum* / Alexandru D. Asandei / Phillip D. Hustad)
- **Polymers for Biomedical Applications I** (*Scott Michael Grayson* / Matthew L. Becker / Jean-Christophe Leroux)
- **Polymers for Biomedical Applications II** (*Theresa M. Reineke* / David M. Haddleton / Laura L. Kiessling)
- **Hybrid Systems** (*Patrick R.L. Malenfant* / Alex Adronov / Jennifer N. Cha)
- **Polymers in Nanomaterials** (*Rachel K. O'Reilly* / Valerie Sheares Ashby / Robert B. Grubbs)

- **Functional Materials**
  (*Eva M. Harth* / David E. Bergbreiter / Wilhelm Huck)
- **Polymers for Advanced Materials Applications**
  (*Martin Heeney* / Douglas R. Robello / E. Bryan Coughlin)
- **Novel Polymeric Structures I**
  (*David L. Green* / Kenneth R. Carter / Christopher W. Bielawski)
- **Natural and Synthetic Self-Assembling Systems**
  (*J. Paul Armistead* / Heather D. Maynard / Stuart J. Rowan)
- **Novel Polymeric Structures II**
  (*Gerald O. Brown* / Andrew B. Lowe / D. Tyler McQuade)
- **Biological Mimics**
  (*Sarah L. Goh* / Kristi S. Anseth / Marcus Weck)
- **Development and Application of New Polymeric Reactions**
  (*Katherine Aubrecht* / Alan E. Rowan / Krzysztof Matyjaszewski)

PROTEIN TRANSPORT ACROSS CELL MEMBRANES
IL CIOCCO
LUCCA (BARGA), ITALY
JUN 10-15, 2007
CARLA KOEHLER &
JUERGEN SOLL, CO-CHAIRS
TASSOS ECONOMOU &
REID GILMORE, CO-VICE CHAIRS

- **Import into Organelles**
  (*Gunnar von Heijne* / Ralph Erdmann / Enrico Schleiff / Walter Neupert / Dennis Voelker)
- **How to Pass through the Translocon**
  (*Jim Whelan* / Danny Schnell / Toshiya Endo / Tassos Economou)
- **The Intermembrane Space**
  (*Nikolaus Pfanner* / Kai Hell / Kostas Tokatlides / Agnieszka Chacinska)
- **Trafficking in Atypical Systems**
  (*Tony Pugsley* / Trevor Lithgow / Francoise Jacob-Dubuisson / Geoffrey McFadden)
- **Molecular Basis of Disease Related to Trafficking**
  (*J.L. Brodsky* / Steve Claypool / Dan N. Hebert / Yukio Fujiki)
- **Getting to Translocons I**
  (*Ida van der Klei* / Ken Cline / Tracy Palmer / Danja Schuenemann)
- **Getting to Translocons II**
  (*Richard Wagner* / Alison Baker / Shou-ou Shan)
- **The Eukaryotic Sec-Translocon: Different Approaches and Different Views**
  (*Roland Beckmann* / Arnold Driessen / Irmi Sinning / Art E. Johnson)
- **Integration of Proteins into Membranes**
  (*Colin Robinson* / Rosemary Stuart / Ross Dalbey / Tom Silhavy)

PROTEINS
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUN 17-22, 2007
CHRISTOPHER HILL &
GARY PIELAK, CO-CHAIRS
JACQUELYN FETROW &
TERRENCE OAS, CO-VICE CHAIRS

- **Keynote Talks: TBA**
  (*Terrence Oas* / Jeffery W. Kelly / *Jacquelyn Fetrow* / X. Sunney Xie)
- **Protein Chemistry and Biophysics in Cells**
  (*Lila Gierasch* / Patricia Clarke / Jonathan Weissman / James Bardwell / Philipp Selenko)
- **Motion and Function**
  (*Carol Post* / Ivet Bahar / Dorothee Kern / Michele Vendruscolo)
- **Disorder, Aggregation, Kinetic Stability, and Disease**
  (*Andrew Miranker* / Wilfredo Colón / Ron Kopito / Rohit Pappu / Roland Riek / Jose Sanchez-Ruiz)
- **Membrane Proteins**
  (*Stephen Betz* / William Clemons / Volker Dötsch / Eduardo Perozo)
- **Protein Networks and Complexes**
  (*Susan Baxter* / Tom Alber / Leslie Poole / James Bowie / Trey Ideker)
- **Modification, Stress and Targeting**
  (*Mary Munson* / Brenda Schulman / Ursula Jakob / James Hurley)
- **Protein Design, Modeling and Prediction**
  (*Stephen Mayo* / David Baker / Homme Hellinga / Hak-Sung Kim)

QUANTUM CONTROL OF LIGHT AND MATTER
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 12-17, 2007
PHILIP BUCKSBAUM &
DAVID TANNOR, CO-CHAIRS
YARON SILBERBERG, VICE CHAIR

- **New Trends in Quantum Control**
  (*Moshe Shapiro* / Peter Zoller)
- **Learning and Chemical Control**
  (*Herschel Rabitz* / Marcos Dantus / Roseanne Sension / Michael Spanner)
- **Quantum Control and Quantum Information**
  (Chris Monroe / Mikhail Lukin)
- **Quantum Control in Chemistry and Biology**
  (*Gustav Gerber* / Graham Fleming / Shaul Mukamel / Dwayne Miller)
- **Control in Spectroscopy**
  (*Paul Brumer* / Tobias Brixner / Steven Cundiff)
- **Attophysics**
  (*Pierre Agostini* / Paul Corkum / Ken Schafer / Johan Mauritsson)
- **Quantum Control of New Physical Frontiers**
  (*Ronnie Kosloff* / Steffen Glaser)
- **Strong Field Quantum Control**
  (Matthias Wollenhaupt / Marc Vrakking / Benjamin Sussman / Christoph Meier)
- **Control of Many Electrons**
  (Hardy Gross)

RADIATION & CLIMATE
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 29-AUG 3, 2007
WILLIAM COLLINS &
PHILIP RUSSELL, CO-CHAIRS
QIANG FU &
CHRISTIAN JAKOB, CO-VICE CHAIRS

- **Keynotes: Properties of Clouds from Multiple Sensors**
  (Graeme Stephens / Robin Hogan)
- **The Climatic Role of Mixed-Phase Clouds**
  (Greg McFarquhar / Ann Fridland / Alexei Korolev)
- **Multi-Scale Models of Cloud Systems**
  (David Randall / Chris Bretherton)
- **Properties of Aerosols from Multiple Sensors**
  (Jens Redemann / Oleg Dubovik / Brian Cairns)
- **Regional Aerosol Models: Simulation of Chemical Weather**
  (Greg Carmichael / Jerome Fast)
- **New Theory and Observations of Cloud/ Aerosol Interactions**
  (Rob Wood / Bill Conant / Thanos Nenes)
- **Challenges in Earth System Modeling**
  (Peter Cox / Toshihiko Takemura / Graham Feingold)
- **Measurement and Modeling of the Changing Cryosphere**
  (Timothy Garrett / Charles Zender)

RADICALS & RADICAL IONS IN CHEMISTRY & BIOLOGY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 1-6, 2007
JAMES TANKO, CHAIR
ARMIDO STUDER, VICE CHAIR

- **Radicals in Synthesis I**
  (Thorsten Bach / Louis Fensterbank / Uta Wille)
- **Polymers and Materials**
  (Krzysztof Matyjaszewski / Richard Weiss / Silas Blackstock)
- **Radicals in Synthesis II**
  (Mick Sherburn / Chaozhong Li)
- **Reaction Mechanisms and Kinetics I**
  (Joe Dinnocenzo / Kim Baines)
- **Radicals, Radical Ions, and Electron Transfer in Biology**
  (Marc Robert / Marc Greenberg / Michele McGuirl)
- **Reaction Mechanisms and Kinetics II**
  (Osvaldo Lanzalunga / Fran Cozens / Matt Platz)

SMALL INTEGRIN-BINDING PROTEINS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
AUG 5-10, 2007
NEAL FEDARKO &
CECILIA GIACHELLI, CO-CHAIRS
MARC MCKEE &
SUSAN RITTLING, CO-VICE CHAIRS

- **Binding Consequences**
  (*Neal Fedarko* / Joanne Murphy-Uhlrich / Elizabeth A. Komives)

- **The SIBLING and CCN Families: The Inside Story**
  (*Jaro Sodek* / Mari Shinohara / Maurice Ringuette / Benard Perbal)
- **Genomic and Cis-Regulatory Analysis of SIBLING & CCN Genes**
  (*Steve Harris* / Masaki Noda / Margarette Goppelte-Struebe)
- **SIBLINGs and Cancer**
  (*Vincent Castronovo* / Akeila Bellahcene / Alison Allan / Susan Rittling)
- **Bioactive Fragments**
  (*Cecilia Giachelli* / Lucy Liaw / Dennis Clegg / Vijaya Rao)
- **CCNs and Cancer**
  (*David Brigstock* / H. Phillip Koeffler / Mauhara Takigawa / Min-Liang Kuo / Sushanta Banerjee)
- **SIBLINGs/CCNs & Normal Physiology**
  (*Jerry Feng* / Susan Schiavi / Ernie Canalis)
- **Inflammation and Other Hot Topics**
  (*David Denhardt* / Dennis Bruemmer / Lester Lau / Marta Scatena / Kathryn Wang)

SOLID STATE CHEMISTRY II
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
SEP 2-7, 2007
EVGENY ANTIPOV, CHAIR
MARTIN JANSEN, VICE CHAIR

- **Materials for Energy**
  (*Bernard Raveau* / Joachim Maier / Claude Delmas)
- **Solids on the Nanoscale**
  (*Mercouri Kanatzidis* / Jing Li / Malcolm Green / Andreas Stein)
- **New Materials for Heterogeneous Catalysis**
  (*Miguel Alario-Franco* / Robert Shlögl / Kenneth Poeppelmeier)
- **Advanced Characterization**
  (*Gustaaf Van Tendeloo* / Juan Manuel Perez-Mato / Joke Hadermann)
- **Molecular and Bio-Solids**
  (*Sergei Aldoshin* / Elena Boldyreva / Marina Petrukhina)
- **Framework and Cage Compounds**
  (Andrei Shevelkov / Sven Lidin)
- **Advances in Theory of Solids**
  (*Juri Grin* / Miroslav Kohout)
- **New Horizons for Oxides**
  (*Peter Battle* / Martha Greenblatt / Patrick Woodward)
- **Magnetic Materials**
  (*Paul Attfield* / Vitalij Pecharsky / Antoine Maignan)
- **Spin Correlations in Solids**
  (Frank Steglich / Daniil Khomski)
- **Fascinating Chemistry of Nitrides**
  (*Martin Jansen* / Rüdiger Kniep / Frank DiSalvo)

STAPHYLOCOCCAL DISEASES
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 2-7, 2007
MATHIAS HERRMANN &
HARALD LABISCHINSKI, CO-CHAIRS
KENNETH BAYLES &
BARRY KREISWIRTH, CO-VICE CHAIRS

- **Frontiers of Research in Staphylococci**
  (*Richard A Proctor* / Richard Novick / Gursharan S. Chhatwal)
- **Animal Models, virulence, and Host Defense Evasion**
  (*Philippe Moreillon* / Yok-Ai Que / Michael D. Menger / Frank D. Lowy)
- **Novel Strategies to Combat Staphylococcal Infections**
  (*Hans Georg Sahl* / Heike Broetz-Oesterhelt / Annaliesa Anderson / Neeloffer Mookherjee)
- **Staphylococcal Virulence Factors and Host Cell Interaction**
  (*Magnus Hook* / Heiko Herwald / Dominique Missiakas / Triantafyllos Chavakis)
- **Immune Mechanisms in Staphylococcal Disease**
  (*Jean C. Lee* / Victor Nizet / Tammy Kielian / Joos van Strijp)
- **System Biology of Staphylococci**
  (*Jodi Lindsay* / Brice Felden / Matthias Heinemann / Makoto Kuroda)
- **Bacterial Physiology and Metabolism**
  (*Greg Somerville* / Paul Williams / Friedrich Goetz / Dorte Frees)
- **Biofilm Growth of Staphylococci: Implications on Regulation and Metabolism**
  (*Dietrich Mack* / Johannes Knobloch / Kimberly Jefferson / George O'Toole)
- **Controversies / Hot Topics**
  (*Georg Peters* / *Steven J. Projan*)

STEM CELLS & CANCER
BIG SKY RESORT
BIG SKY, MT
SEP 9-14, 2007
MICHAEL CLARKE, CHAIR
MAARTEN VAN LOHUIZEN, VICE CHAIR

- **Keynote Talk: Understanding the Molecular Basis of Oncogenesis**
  (Robert Weinberg)
- **Understanding the Molecular Basis of Oncogenesis**
  (Sturart Orkin / David Scadden / Philip Beachy / Ihor Lemishka)
- **Cellular Hierarchy of Normal Blood and Leukemia Cells**
  (Irving L. Weissman / D. Gary Gilliland)
- **Identification of Self-Renewing Cells in Solid Organs**
  (Connie Eaves / Jane Visvader / Nobuko Uchida / Ronald Dephinho)
- **Identification of Cancer Stem Cells in Leukemia and Brain Tumors**
  (Giulio Draetta / Peter Dirks / Jeremy Rich)
- **Stromal Cell Interactions with Self-Renewing Cancer Cells**
  (Mina Bissel / Patrick Brown / Stephen Weiss)
- **Late Breaking Abstracts**
  (*Fredereick W. Alt*)
- **Therapies Against Cancer Stem Cells 1**
  (Napoleone Ferrara / Charles Sawyer / A. Thomas Look / Craig Jordan)
- **Therapies Against Cancer Stem Cells 2**
  (Barbara Weber / Timothy Hoey / Catriona Jamieson)

STRESS PROTEINS IN GROWTH, DEVELOPMENT & DISEASE
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
AUG 19-24, 2007
PETER WALTER, CHAIR
BERND BUKAU, VICE CHAIR

- **Keynote Talk: Protein Misfolding in Stress, Aging, and Neurodegenerative Disease**
  (Richard Morimoto)
- **Aging and Longevity**
  (Cynthia Kenyon / Lenny Guarente / Thomas Nystrm)
- **Cell Biology and Mechanism**
  (Yoshinori Ohsumi / Sebastian Bernales / Jeff Brodsky / Adi Kimchi / Kazuhiro Nagata)
- **Immunity, Infection and Cancer**
  (Lauri Glimcher / Hidde Ploegh / Chris Nicchitta / Ana Marie Cuervo)
- **Metabolic and Nutritional Stress**
  (David Ron / Kaveh Ashrafi / Benjamin Tu)
- **Oxidative and Metal-Catalyzed Damage**
  (Ursula Jakob / Sabeeha Merchant / Dennis Thiele)
- **Protein Conformation Diseases**
  (Susan Lindquist / Adriano Aguzzi / Jeff Kelly / Jonathan Weissman)
- **Role of Stress Proteins**
  (Judith Frydman / Elizabeth Craig / Kevin Morano / Elizabeth Vierling)
- **Stress Sensing and Response**
  (Lea Sistonen / Carol Gross / Jon Lis / Jason Brickner / Hana El Samad)

STRUCTURAL, FUNCTIONAL & EVOLUTIONARY GENOMICS
WELLCOME TRUST CONFERENCE CENTRE
HINXTON, CAMBRIDGE, UNITED KINGDOM
JUL 29-AUG 3, 2007
EUGENE KOONIN, CHAIR
JOEL BADER, VICE CHAIR

- **Structural, Functional and Evolutionary Genomic**
  (*Eugene Koonin* / *Joel Bader*)
- **Keynote Talk 1: Evolution of Genome Complexity**
  (Michael Lynch)
- **Keynote Talk 2: TBA**
  (Naama Barkai)
- **Structural Genomics**
  (*Christine Orengo* / Rob Russell / Jeffrey Skolnick / Adam Godzick)
- **Network Biology and Evolution**
  (*Sarah Teichmann* / Hannah Margalit / Jose Pereira-Leal / Trey Ideker / Greg Wray)
- **Clocks and Trees**
  (*Lindell Bromham* / Andrew Rambaut / Russell Gray / Phil Donaghue / Zihen Yang)
- **Comparative Genomics of Gene Expression and Evolution of Non-Coding Sequences**
  (*Manolis Dermitzakis* / Gerton Lunter / Carlos Bustamante / Leonid Kruglyak / Greg Gibson)
- **Major Evolutionary Transitions**
  (*Purificacion Lopez-Garcia* / William Martin / J. Peter Gogarten / L. Aravind / Franz Lang)
- **Evolution, Biodiversity, and Metagenomics**
  (*Camilla Nesbo* / Forest Rohwer / Christa Schleper / Steven Hallam / Oded Beja)
- **Viruses, Mobile Elements and Cellular Evolution**
  (*Valerian Dolja* / Jurgen Brosius / Roger Henrdix)

- **Functional Genetic Screens**
  (Andrew Fraser / Jussi Taipale / Brenda Andrews / Tony Hyman)
- **Synthetic Genomics**
  (Jeff Boeke)

SUPERCONDUCTIVITY
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 9-14, 2007
NICOLE BONTEMPS, CHAIR
FUCHUN ZHANG, VICE CHAIR

- **BCS at the Frontier**
  (*A. Leggett* / M. Alford / W. Ketterle / Y. Lee)
- **Cold Atoms Merge with Condensed Matter**
  (*G. Strinati* / T. Esslinger / R. Hulet / C. Salomon)
- **Clues for Long Standing Problems: Mechanism of Superconducivity, Pseudogap, Coexisting/Competing States**
  (*G. Deutscher* / K.A. Müller / A.Yazdani)
- **Two Energy Scales in the Superconducting State of Cuprates**
  (*H. Takagi* / J.C. Davis / Z.X. Shen)
- **Theory of Strong Correlations in the Hubbard Model: Application to Superconductors (Cuprates, Organics)**
  (A. Georges / K. Haule / T. Maier / A.M. Tremblay)
- **Unconventional Superconductivity, Magnetism, Quantum Criticality in Heavy Fermions**
  (*M. Sigrist* / L. Greene / C. Pépin / O. Stockert / H.Q. Yuan)
- **Newly Discovered Superconductors, Conventional Superconductivity?**
  (*H. Alloul* / Z. Hiroi / M. Ortolani / S. Saxena)
- **Superconductivity in Confined Geometry**
  (H. Bouchiat / J.M. Triscone)
- **Latest Developments and New Prospects**
  (*D. Van Der Marel* / K. Kitazawa)

THIN FILM & CRYSTAL GROWTH MECHANISMS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 24-29, 2007
PETER VEKILOV, CHAIR
JONAH ERLEBACHER, VICE CHAIR

- **Fundamentals**
  (*Peter Vekilov* / Ellen Williams / Alexander Chernov)
- **Biomineralization**
  (*Christine Orme* / Joanna Aizenberg / James DeYoreo)
- **Protein Crystallization**
  (*Naomi Chayen* / Katsuo Tsukamoto / Jonathan Doye)
- **Self-Assembly of Colloids**
  (Paul Chaikin / Bartosz A. Grzybowski / Alfons van Blaaderen)
- **Nucleation Mechanisms**
  (*James Lutsko* / Anatoly Kolomeisky)
- **Crystallization in Pharmacy and Medicine**
  (*Michael Doherty* / Brian Johnson / Leslie Leiserovitz / Ronald Nagel)
- **Surface Morphology**
  (*Kristen Fichthorn* / Dionisios Margetis / Vesselin Tonchev)
- **Organic Layers**
  (*Melissa Hines* / Margret Giesen)
- **Thin Film Growth**
  (*Jonah Erlebacher* / Giovanni Constantini / John Venables)

THREE DIMENSIONAL ELECTRON MICROSCOPY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 24-29, 2007
PHOEBE STEWART, CHAIR
WERNER KUEHLBRANDT, VICE CHAIR
STEPHEN FULLER, CHAIR ELECT FOR 2009

- **Visualizing Biological Processes with 3D EM**
  (*Phoebe Stewart* / Tony Crowther / Ron Milligan)
- **DNA Transactions**
  (Francisco Asturias / Eva Nogales)
- **RNA and Ribosome Transactions**
  (B.V.V. Prasad)
- **Protein Filament Activities**
  (Dorit Hanein)
- **Poster Presentations and Discussion I**
  (*Sharon Wolf*)
- **Membrane Proximal Events**
  (*Werner Kuehlbrandt* / Bernard Heymann / Stephen Fuller)
- **Technical Advances**
  (Harald Rose / Jens Meiler)
- **Poster Presentations and Discussion II**
  (*Esther Bullitt*)

TIME-DEPENDENT DENSITY-FUNCTIONAL THEORY
COLBY COLLEGE
WATERVILLE, ME
JUL 15-20, 2007
KIERON BURKE &
CARSTEN ULLRICH, CO-CHAIRS
ANGEL RUBIO, VICE CHAIR

- **Fundamentals of TDDFT**
  (*E.K.U. Gross* / Giovanni Vignale / Meta van Faassen)
- **Photochemistry and Excited-State Dynamics**
  (*Mark Casida* / Giulia Galli / Annabella Selloni / Sergei Tretiak)
- **Optical Spectra of Materials: From Nanocrystals to Solids**
  (*Andreas Goerling* / James Chelikowsky / Lucia Reining)
- **Nonadiabatic Electron-Ion Dynamics**
  (*Evert J. Baerends* / Oleg Prezhdo / Roi Baer / Tchavdar Todorov)
- **Single-Molecule Transport**
  (*Harold Baranger* / Roberto Car / Stefan Kurth)
- **Strong-Field Phenomena in Atoms and Molecules**
  (*Andre Bandrauk* / Manfred Lein / Thomas Brabec / Stephan Kuemmel)
- **New Functionals**
  (*Giovanni Vignale* / David Langreth / Andreas Goerling)
- **Charge Transfer in Biomolecules**
  (*Nicola Marzari* / Filipp Furche / Troy Van Voorhis / Neepa Maitra)
- **New Computational Developments**
  (*Angel Rubio* / Stefano Baroni / Miguel Marques)

TISSUE REPAIR & REGENERATION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 17-22, 2007
JACK GAULDIE, CHAIR
LUISA DIPIETRO, VICE CHAIR

- **Models of Tissue Repair**
  (*Judy Abraham* / Paul Martin / Tom Mustoe)
- **Cell Migration and Wound Closure**
  (*Fred Grinnell* / Pierre Coulombe / Bill Parks / Liz Fini / Fred Grinnell)
- **Angiogenesis, Lymphangiogenesis and Neurogenesis**
  (*Jeff Davidson* / Nancy Boudreau / Holger Gerhardt / Kari Alitalo / Shahin Rafii / Larry Benowitz)
- **Inflammation/Stress Molecular Triggers**
  (*Luisa DiPietro* / Chanden Sen / Hynda Kleinman / Walter Wahli / Hannu Larjava)
- **Regeneration**
  (*Maria Sibilia* / Ellen Heber-Katz / Pascale Dufourcq)
- **Growth Factors in Repair**
  (*Kathy Flanders* / Sabine Werner / Gary Grotendorst / Jeff Hubbell / Ping Wei / Lillian Nanney)
- **Scarring and Regeneration**
  (*Alain Mauviel* / David Warburton / Snorri Thorgeirsson / Erwin Bottinger / Paul Noble / Bob Strieter)
- **Stem Cells and Regeneration/Repair**
  (*Rick Bucala* / Barry Stripp / Dianne Krause / Eric Neilson / George Cotsareli)
- **Bioengineering**
  (*Molly Stoichet* / Anthony Atala / Molly Shoichet)

TOXICOGENOMICS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 24-29, 2007
CINDY AFSHARI &
CHRISTOPHER BRADFIELD, CO-CHAIRS
MARTYN SMITH &
CRAIG THOMAS, CO-VICE CHAIRS

- **Keynote Session: Toxicogenomics - A Tool to Probe Disease and Mechanisms of Toxicity**
- **Impact of Genomics in Respiratory Toxicology**
- **Kidney Disease and Nephrotoxicity Biomarkers**
- **Network Analysis and Integration**
- **Vascular Toxicity, Network Biology and Biomarkers**
- **Hepatotoxicity and Genomics Exploration**
- **Human Susceptibility and Population Analysis**
- **Epigenetic Toxicology**
- **Predictive Toxicology: Applications and Perspective**

TUBERCULOSIS DRUG DEVELOPMENT
MAGDALEN COLLEGE
OXFORD, UNITED KINGDOM
AUG 26-31, 2007
VALERIE MIZRAHI, CHAIR
ERIC RUBIN &
BALA SUBRAMANIAN, CO-VICE CHAIRS

- **Strategies for the Development and Deployment of New Antibiotics**
  (*Valerie Mizrahi* / Christopher Walsh / Paul Farmer / Nulda Beyers)
- **Lessons from the Broad Spectrum Area**
  (*Bala Subramanian* / Trevor Trust / Steve Projan / Richard Lee)
- **Scientific Issues in Early Clinical Development**
  (*Clif Barry* / David McNeeley / Gerry Davies / Anne Lenaerts)
- **New Target Areas**
  (*Harvey Rubin* / Peter Tonge / Cindy Dowd)
- **Environmental Responses and Drug Tolerance**
  (*David Sherman* / Bruce Levin / Kevin Pethe)
- **Targeting Macromolecular Synthesis and Turnover**
  (*Thomas Dick* / Carl Nathan / Rajesh Gokhale / Thomas Keller)
- **Regulation and Metabolism**
  (*Tom Alber* / Jim Sacchettini / Helena Boshoff)
- **New Technologies**
  (*Eric Rubin* / John Overington / Chris Abell / Sarah Fortune / Tanya Parish)
- **Getting Drugs to their Targets**
  (*Ken Duncan* / Paul Tulkens / George Drusano / Chris Lipinski)

VIRUSES & CELLS
TILTON SCHOOL
TILTON, NH
JUN 3-8, 2007
DIANE GRIFFIN, CHAIR
ROZANNE SANDRI-GOLDIN, VICE CHAIR

- **Entry and Receptors**
  (*Jeff Bergelson* / *Bernard Moss* / Felix Rey / Terence Dermody / Katya Heldwein / Roselyn Eisenberg)
- **RNA Virus Translation, Transcription and Replication**
  (*Ralf Bartenschlager* / *Doug Lyles* / Andrea Brmarnik / Ann Palmenberg / Didier Poncet / Sean Whelan)
- **DNA Virus Transcription, Translation and Replication**
  (*Ian Mohr* / *Deborah Spector* / Matthew Weitzman / Sandra Weller / Blossom Damania / Robert Kalejta)
- **Dynamics of Intracellular Trafficking**
  (*Karla Kirkegaard* / Xiaowei Zhuang / Urs Greber / Gregory Smith / Michael Way)
- **Special Lecture: 50th Anniversary of the Discovery of Interferon**
  (Otto Haller)
- **Cellular Response to Infection and Virus Counter-Response**
  (*Otto Haller* / *John Hiscott* / Takashi Fujita / Frank Chisari / Adolfo Garcia-Sastre / Marco Colonna)
- **Cellular Inhibition of Virus Replication and Virus Countermeasures**
  (*Michelle Barry* / *Ganes Sen* / Shou-Wei Ding / Richard Randall / Joseph Sodroski / Karen Mossman)
- **Assembly, Budding and Release**
  (*Gabriella Campadelli-Fiume* / *Joel Baines* / Anette Schneemann / Alasdair Steven / Caron Carter / Venigallo Rao)
- **Immune Response and Pathogenesis**
  (*Kim Hasenkrug* / *Skip Virgin* / Troy Randall / Daniel Douek / Michaela Muller-Trutwin / Kathy Spindler)
- **Evolution, Epidemiology, Prevention and Therapy**
  (*Andrew Davison* / *Francine McCutchan* / Eddie Holmes / Mark Young / Claude Fauquet / Richard Whitley)

VISUALIZATION IN SCIENCE & EDUCATION
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 1-6, 2007
ROY TASKER &
CHRISTOPHER WATTERS, CO-CHAIRS
SHAARON AINSWORTH &
ARTHUR OLSON, CO-VICE CHAIRS

- **Interpreting Visual Data with Difficulty**
  (Bart Anderson / Eric Scerri)
- **Creating Visualizations of Biological Complexity**
  (Andrew Hanson / David Goodsell / Graham Johnson)
- **Issues in Visualizing Chemical Concepts**
  (Michael Stieff / Karl Harrison)
- **Visualizing Physical Phenomena using Interactive Media**
  (Chandrajit Bajaj / Gabriela Weaver / Pablo Morales)
- **Multidisciplinary Approaches to Visualization in Science Education**
  (Mary Shultz / Jerry Honts / past Visionary Grant recipients)
- **Effective Data Presentation for Museum Audiences and Informal Learning**
  (Donna Cox / Ka Chun Yu / Martin Storksdiek)
- **Improving Public Understanding of Science Through Visualization: A Panel Discussion**
  (Robin Heyden / Rebecca Perry / Larry Gonick)
- **Effective Visualizations in the GeoSciences**
  (Tim Spangler / Kim Kastens / Janice Gobert)
- **Visual Problem Solving**
  (Peter Atkins)

VITAMIN B_{12} & CORPHINS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 1-6, 2007
WILFRED VAN DER DONK, CHAIR
BERNHARD KRAEUTLER, VICE CHAIR

- **New Developments in Mechanism and Structure**
  (*Bernhard Kräutler* / Bernard Golding / Michael Wiener)
- **Medical Aspects of B_{12}**
  (*Søren Moestrup* / Brian Fowler / Mette Madsen / Joshua Miller / David Rosenblatt)
- **Spectroscopy and Theory**
  (Thomas Brunold / Roseanne Sension / David Smith)
- **Mechanisms of B_{12}-dependent Enzymes**
  (*Rowena Matthews* / *Cathy Drennan* / Ruma Banerjee / Tom Bobik / Angela Fleischhacker / George Reed)
- **Corphins**
  (*Rolf Thauer* / Evert Duin / Stephen Ragsdale / Marc Zimmer)
- **Biosynthesis and Uptake**
  (*Tetsuo Toraya* / Alison Smith / Michi Taga / Martin Warren)
- **B_{12} in Human Health**
  (*Ralph Green* / Andrew McCaddon / Charles Grissom / Rima Obeid)
- **Model Systems**
  (*Ken Brown* / Rudi van Eldik / Kris McNeill / Roger Alberto)
- **Perspectives and Prospects**
  (*Wilfred van der Donk* / John Roth / Ebba Nexo)

X-RAY PHYSICS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
AUG 5-10, 2007
KENNETH FINKELSTEIN, CHAIR
JUNICHIRO MIZUKI, VICE CHAIR

- **Science Frontiers Using New X-Ray Sources**
  (*H. Dosch* / T. Ishikawa / J.R. Schneider)
- **Ultra-Short Pulse X-Ray Science**
  (*D. Reis* / A. Cavalleri / D. Villeneuve / H. Chapmann)
- **Frontier Applications for Soft X-Rays**
  (*P. Abbamonte* / George Sawatzky / C. Schüßler-Langeheine)
- **Coherence and Phase Imaging**
  (*Q. Shen* / F. Pfeiffer / P. Fenter / M. Giglio)
- **New and Novel X-Ray Scattering**
  (*J. Goulon* / W. Bailey / T. Arima)
- **Materials Science with Nano-Scale Beams**
  (*D. Bilderback* / A. Macrander / M. McMahon / Y. Terada)
- **Hot Topics**
  (S. Gruner / A. Bosak / Y. Shvyd'ko)
- **X-Rays in Medicine, Life, and Environmental Sciences**
  (*A. Bravin* / Y.Sasaki / Z. Zhong / K. Boyce)

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POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSOR, Gene Therapy Program, Louisiana State University Health Sciences Center. The Gene Therapy Program at the Louisiana State University Health Sciences Center (LSUHSC) in New Orleans, Louisiana, invites applications for a tenure-track faculty position at the level of Associate Professor or Assistant Professor. Applicants must hold a Ph.D. and/or an M.D. degree. The position would suit an individual with interest in gene delivery and/or vaccination for modulation or prophylaxis of infectious or neoplastic disease, areas of current strength within the Program. We are particularly interested in candidates who have demonstrated translational research capacity, and intramural funding is available to support developmental and ongoing translational studies. Current external funding held by Program members exceeds $23 million, mostly from the National Institutes of Health, and includes federal and state P01 awards. The Program was founded in 2000 and is partnered with Tulane University Health Sciences Center and LSU-Shreveport in the state-funded Louisiana Gene Therapy Research Consortium (LGTRC). The Program is located in the new Clinical Sciences Research Building at LSUHSC in space adjacent to the Stanley Scott Cancer Center. The Program currently has seven faculty members, several adjunct faculty, funds three state-of-the-art core facilities in morphology and imaging, microarray and bio-informatics and vector development, and oversees a BSL-3 facility. State-of-the-art immunology and proteomics cores have also been developed at LSUHSC. Through the LGTRC, we will have direct access to wet laboratory space in the New Orleans BioInnovation Center and a good manufacturing practice facility currently under construction that will facilitate the development of clinical trials arising from Program research. Applicants should send an e-mail including curriculum vitae to: **Dr. Alistair Ramsay, Program Director** at **e-mail: slaure@lsuhsc.edu.** *LSUHSC is an Equal Opportunity/Affirmative Action Employer.*

ENDOWED CHAIR in the BIOCHEMICAL SCIENCES
Department of Chemistry
University of Missouri-Rolla

Distinguished scientists are encouraged to apply for the **Richard K. Vitek**/Foundation for Chemical Research (FCR) Endowed Chair in Biochemistry, including the areas of bioorganic, biophysical, or biomaterials chemistry at the University of Missouri-Rolla (UMR). The new position carries a very generous endowment, which can be used in part to support the research of the Chair. The Richard K. Vitek/FCR Endowed Chair in Biochemistry will provide important leadership for UMR's targeted growth in the biosciences. A new biosciences building has been established by the state of Missouri as the next capital improvement project for higher education.

The successful candidate should have a Doctorate in chemistry, biochemistry, or a related field, and have an outstanding international reputation and publication record, and a substantial record of extramural funding. This search has been extended and review of applications will resume on March 15, 2007, and continue until the position is filled. For further information, we encourage you to visit our **website: http://chem.umr.edu** or contact **Professor Jay A. Switzer** at **e-mail: jswitzer@umr.edu.**

Please submit curriculum vitae and short summaries of past research accomplishments and future research directions to: **Human Resource Services, Reference Number: 00033199, University of Missouri-Rolla, 1870 Miner Circle, Rolla, MO 65409-1050.**

UMR is an Affirmative Action/Equal Employment Employer. Women, minorities, and persons with disabilities are encouraged to apply.

POSITIONS OPEN

USDA ARS Agricultural Research Service
www.ars.usda.gov

AGRICULTURAL RESEARCH SERVICE
Website: http://www.ars.usda.gov

United States Department of Agriculture, Agricultural Research Service (ARS), Beneficial Insect Introductions Research Laboratory in Newark, Delaware, seeks a full-time, permanent **RESEARCH ENTOMOLOGIST** (GS-12/13/14) to work on biological control of emerald ash borer and other invasive insect species. Ph.D. in entomology or other biological science with strong emphasis on ecology is preferred. Requires training or experience in design and conduct of field experiments on spatial and temporal population dynamics of insects and their natural enemies, as well as mathematical modeling and statistical analysis of resulting data. Annual salary is $66,914 to $122,235 plus benefits. Application procedures and qualifications for the position are available at **website: http://www.usajobs.com.** Announcement number ARS-X7E-0084. If you need a printed copy mailed please call **telephone: 302-731-7330, ext. 222.** *U.S. citizenship is required.* Applications must be received by March 23, 2007. *ARS is an Equal Opportunity Employer and Provider.*

FACULTY POSITION
Temple University School of Medicine
Department of Biochemistry

The Department of Biochemistry, Temple University School of Medicine **(website: http://www.temple.edu/medicine/)** invites applications for a tenure-track faculty position. The successful candidate will be expected to develop a strong, externally funded research program that effectively interfaces with one or more of the departmental areas of research focus as well as with existing research centers within the School of Medicine. Rank will be **ASSISTANT** or **ASSOCIATE PROFESSOR,** depending on experience and credentials. Teaching responsibilities will be in departmental courses in medical and graduate education. Applicants should send a letter outlining current and future research plans, curriculum vitae, and names of three references via **e-mail: ppileggi@temple.edu** or by mail to:

Dr. Joanne Orth, Senior Associate Dean for Faculty Affairs
c/o Ms. Patricia Pileggi
Office of Faculty Affairs
Temple University School of Medicine
3420 North Broad Street, 108 MRB
Philadelphia, PA 19140

Temple University is an Affirmative Action/Equal Opportunity Employer and strongly encourages applications from women and minorities.

FACULTY POSITIONS
All Areas of Life Science
National Central University, Taiwan

The Department of Life Science at National Central University, Taiwan, is seeking applications for Faculty Positions at all ranks. Candidates must have a Ph.D. degree in life sciences-related fields and two or more years of postdoctoral or equivalent research experience. To guarantee full consideration, candidates should submit applications by April 15, 2007. To apply, submit a letter of intent, curriculum vitae with publication lists, reprints of representative publications (one to three), brief teaching and research plans, and have three letters of recommendation sent to: **Recruitment Committee, Department of Life Science, National Central University, 300 Jhong-Da Road, Jhong-Li, Taiwan. E-mail: slcj@ncu.edu.tw, fax: 886-3-4228482.** The search will remain open until the position is filled.

FOREIGN FACULTY FACE CHALLENGES

Many foreign-born scientists have made the United States their home because the country provides some of the best training and career opportunities worldwide. But life as a foreign scientist is not without its challenges. **By Laura Bonetta**

Yuri Lazebnik

Shortly after joining William Earnshaw's lab at Johns Hopkins School of Medicine in 1991, Russian-born **Yuri Lazebnik** attended a seminar. Although he did not know the speaker, he could tell from everyone's anticipation of the talk that he was a famous scientist. As the seminar started, Lazebnik discovered the speaker had a heavy foreign accent. "I looked at everyone around me and realized at that moment that if you have something to say and can be understood, it does not matter where you come from," he recalls.

Lazebnik, now a professor at the Cold Spring Harbor Laboratory in Long Island, New York, is one of many foreign-born scientists who emigrated to the United States for their postdoctoral training and decided to stay in the country. The proportion of postdoctoral scholars on temporary visas increased from 37.4 percent in 1982 to 58.8 percent in 2002, outnumbering U.S. citizens and permanent residents. Although many foreign postdocs return to their home countries to land academic positions, many others choose to remain. A survey by the scientific society Sigma Xi (Research Triangle Park, North Carolina) found that the United States was the most attractive place to settle for postdoctoral scholars of all nationalities, regardless of where they earned their Ph.D.s. And the fondness is mutual. A recent report on foreign scholars published by the National Academies of Science (NAS) concluded that, in order to maintain its dominance in science and technology, the United States should continue to recruit the best and brightest international students.

But this does not mean that being a foreign-born scientist in the United States is without challenges. Some of the difficulties are obvious. Immigration red tape, especially in the post 9/11 climate, makes it more difficult for foreign postdocs to find permanent employment in the United States and to travel internationally. Other challenges are not as clearly defined. The Sigma Xi survey found that although international and domestic academic postdoctoral scholars expressed similar satisfaction with their training experience, temporary residents had more limited access to funding sources and to employment opportunities. In addition, the stipends of temporary residents were about 7 percent less than those of citizens. Other studies show that the length of postdoctoral appointments tends to be slightly longer for noncitizens, "maybe because they do not navigate the system as well," says **Chiara Gamberi,** vice chair of the International Committee of the National Postdoctoral Association. "We don't have enough data to know what the effects are." Without a doubt, language barriers, cultural differences, and distance from family and loved ones make the lives of foreigners, in any type of work, more challenging.

> "If you have something to say and can be understood, it does not matter where you come from."

Immigration Woes

After the terrorist attacks of September 11, 2001, the U.S. government introduced a number of new policies and procedures aimed at increasing security in its visa processing system. As a result, almost all visa applicants have to appear for a personal interview at the nearest U.S. consulate, sometimes waiting up to four months to get an appointment. Sometimes applications undergo a second review by the U.S. Department of State in Washington, D.C. A security review process known as Visas Mantis, CONTINUED »

UPCOMING FEATURES

International Careers Report: Science in Europe — March 2

Careers in Cancer Research — April 6

Careers for Postdoc Scientists: Transeferable Careers — April 20

MEDICAL COLLEGE OF WISCONSIN

FACULTY POSITIONS
BREAST CANCER RESEARCH

The Medical College of Wisconsin invites nominations and applications for faculty positions at all levels (Assistant, Associate or Full Professor) to study signal transduction and/or molecular genetic mechanisms involved in cancer. The positions are part of the College's expansion of basic cancer research to complement our state-of-the-art clinical cancer care. Competitive development packages are available for these positions, including an endowed chair in Breast Cancer Research for an established investigator. The successful candidates will obtain a primary appointment in a basic research department and membership in the Cancer Center.

The Medical College of Wisconsin (**www.mcw.edu**) is the largest private research institution in Wisconsin, conducting over $130 million annually in funded research. Over the past several years the College has been among the fastest growing medical schools in the United States in terms of NIH funding. In addition to a strong core of basic biomedical science departments, the Medical College is home to nine federally designated Centers of Biomedical Research. Excellent shared facilities are available for proteomics, imaging, molecular biology, mouse/rat genetics, flow cytometry, mass spectrometry, electron microscopy, X-ray crystallography and NMR. The research and clinical programs benefit directly from strong philanthropic support from cancer survivors, family members, and patient advocates. The College is completing major new research and cancer care facilities, including a Cancer Pavilion and a Basic Research Building housing interdisciplinary research programs.

The Medical College is conveniently located in suburban Milwaukee and is part of an academic medical center that includes nationally distinguished children's and adult hospitals that employ over 13,000 people. The College is located 8 miles west of Lake Michigan with easy access to surrounding communities, lakes, and parks.

Salary and other considerations will be competitive and consistent with the College's commitment to recruiting the best-qualified individual. Applicants should provide curriculum vitae, statement of research interests, and the names and contact information of three references. Please submit application materials, preferable electronically (PDF) to one of the following chairs at **cancersearch@mcw.edu** :

Robert Deschenes, Chair
Dept of Biochemistry
rdeschen@mcw.edu
www.mcw.edu/biochemistry

William Campbell, Chair
Dept of Pharmacology
wbcamp@mcw.edu
www.mcw.edu/pharmtox

Paula Traktman, Chair
Dept of Microbiology/Molecular Genetics
ptrakt@mcw.edu
www.mcw.edu/microbiology

EOE M/F/D/V (www.mcw.edu/hr)

Center for Biopreparedness and Infectious Disease
Department of Microbiology and Molecular Genetics
Tenure Track Position:
Microbial Pathogenesis and Host Response

MEDICAL COLLEGE OF WISCONSIN

Candidates with advanced degrees (MD, PhD, MD/PhD) are invited to apply for a tenure-track Assistant Professorship; outstanding individuals of higher rank will be considered. Investigators interested in the interaction of microbial pathogens with their mammalian hosts are encouraged to respond. We are particularly interested in scientists whose research centers on the mechanisms by which bacterial pathogens interface with cellular functions and manipulate the innate or acquired immune response.

The Center for Biopreparedness and Infectious Disease (CBID) is part of campus wide initiatives to build research programs with relevance for the development of novel therapeutics and vaccines. Members of CBID and the Department of Microbiology and Molecular Genetics actively participate in the Great Lakes Regional Center of Excellence for Biodefense and Emerging Infectious Disease Research. The successful applicant will join a highly interactive and collegial group of well-funded investigators and be expected to establish an independent research program that includes participation in graduate and medical student teaching. Competitive packages with salary support and start-up funds, newly constructed laboratory space and state-of-the-art BSL3 and ABSL3 core facilities will be provided.

Applications will be considered as they arrive but must be received by **March 15, 2007**. Applicants should submit a *curriculum vitae*, statement of research interests and the names of three references **c/o Cathi Kienast** to: **Dr. Dara W. Frank, Director, Center for Biopreparedness and Infectious Disease, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226, E-mail ckienast@mcw.edu; http://www.mcw.edu/microbiology**.

EEO/AA/M/F/D/V

UNIVERSITY OF Cincinnati

Chair, Department of Cell and Cancer Biology

The University of Cincinnati College of Medicine seeks applications and nominations for the position of Professor and Chair, Department of Cell and Cancer Biology. We seek an internationally recognized academic leader with a strong track record of scientific accomplishments, who can enhance current strengths in cell and cancer biology research in the areas of hormone-dependent cancers, cell cycle, environmentally induced cancers, tumor suppressors, cytoskeleton, and signal transduction. This is an exceptional opportunity for someone with vision to lead and expand a prominent academic research unit.

The Department of Cell and Cancer Biology is home to fifteen established cell/cancer biology researchers, including a member of the National Academy of Sciences. Total extramural grant holdings of the faculty place the Department 11th among all US public medical school Cell Biology departments. The Department hosts a vibrant interdisciplinary Cell and Cancer Biology graduate program, with three NIH-funded training grants providing support for many of its trainees. Resources are excellent; the Department is housed in the Frank Gehry-designed Vontz Center for Molecular Studies, with outstanding research space and ancillary facilities. The University of Cincinnati College of Medicine ranks 19th among all public medical schools, with more than $250 million in sponsored program awards.

Interested candidates should submit a comprehensive curriculum vitae and contact information for three references to: **The Office of Faculty and Administrative Affairs, The University of Cincinnati College of Medicine, 200 Albert Sabin Way, Suite 1200, Holmes, Cincinnati, Ohio 45267-0554, ATTN: Cell and Cancer Biology Chair Search**; or e-mail: **marianne.niehaus@uc.edu**. Review of applications will commence immediately and continue until the position is filled.

The University of Cincinnati is an Affirmative Action, Equal Opportunity Employer. Women, minorities, disabled persons, Vietnam era and disabled veterans are encouraged to apply. The U.C. Academic Health Center is a smoke-free work environment.

Chiara Gamberi

"Benefits have to be discussed in the U.S. — in Europe you just have them."

Joel Shulman

required for applicants with a background in one of the sensitive technologies on the Technology Alert List, is behind most of the delays experienced by foreign scientists. Visas Mantis is not a new procedure, but the number of applications being reviewed increased from about a thousand in the year 2000 to 20,000 in 2003 (*Science* **312:**657, 2006).

The process is a source of frustration to many foreign scientists visiting the United States. Last year, Indian chemist Goverdhan Mehta, who serves as president of the International Council for Science, canceled a trip to the University of Florida when his visa application was found in need of further scrutiny. The scientist told the Indian press that he found the review process humiliating and unnecessary.

Although the Mehta case caused a stir in the international scientific community, most visa problems go unheard, and it is impossible to know how many scientists are simply refusing to travel to the United States. Delays in obtaining a visa approval can have particularly damaging consequences for scientists who are working in the United States. "We know of cases where they have gone home for an emergency and cannot get back because of visa problems," says **Wendy White**, director of the Board on International Scientific Organizations at NAS. "They are separated from their families, cannot pay their bills, and sometimes lose their jobs." White oversees NAS's International Visitors Office (http://www7.national-academies.org/visas), set up to help scientists who have been waiting for visa approval for more than three weeks. The office alerts the Department of State of such cases in an effort to expedite the review process.

Fortunately, such problems are getting, by all accounts, less frequent. The number of cases the International Visitors Office at NAS dealt with in 2006 was down to 204 compared to 856 in 2003. And in 2005, the Department of State announced that it increased staffing and streamlined systems to reduce the average time for obtaining Visas Mantis clearance to less than 14 days. "The perception that the U.S. does not welcome foreign students is diminishing," says **Amy Scott**, senior federal relations officer at the Association of American Universities. "I think we are getting back to being seen as a welcoming nation both for students and in terms of faculty opportunities."

But White says more should be done to avoid long delays for visa applications. "We understand the need for security, but perhaps people who have successfully completed the clearance process could be given a special status so that they do not have to undergo these interviews each time they need or want to travel to the United States," she suggests.

Cut Off from Funding

At the moment, tenured faculty positions in the United States are hard to come by, regardless of citizenship. This is in part due to the fact that, as National Institutes of Health Director Elias Zerhouni recently pointed out, the number of scientists in the United States has dramatically increased over the past decade (*Science*, **314:**1088, 2006). But although foreign postdocs now outnumber home grown ones, a report by the Federation of American Societies of Experimental Biology (FASEB) concluded that "there is no evidence that they are taking permanent jobs away from U.S. citizens" (**Garrison et al.** *FASEB J.* **19:**1938, 2005). In fact there are hints that foreign postdocs may have a harder time landing permanent faculty positions than their U.S.-born colleagues.

For one thing, most federal funding sources for postdoctoral training are strictly reserved for U.S. citizens and U.S. permanent residents. This not only translates to lower salaries, on average, for foreign postdocs, but also renders them less competitive. The NAS report, *Addressing the Nation's Changing Need for Biomedical and Behavioral Scientists* (2000), found that postdoctoral participants in the National Research Service Award program, from which foreign scientists are barred, completed their postdoctoral training faster and went on to more successful research careers. In particular, former NRSA fellows were more likely to be successful in competing for NIH grants as independent investigators.

Scientists on temporary visas don't have access to some government jobs, such as principal investigator at the NIH. While there is no evidence that foreign applicants would be less desirable to a university's faculty hiring committee, "it is more complicated to hire foreign faculty because of the paperwork," says Gamberi. Indeed, in industry, foreigner-born postdocs have to go the extra mile to land a position. For the past five years, **Joel Shulman**, adjunct professor of chemistry at the University of Cincinnati and former manager of doctoral recruiting and external relations at Procter & Gamble, has been running a workshop at the annual meeting of the American Chemical Society for foreign nationals who want to remain to work in the United States (http://www.chemistry.org/careers). "To hire you on a permanent basis, employers have to sponsor you for a green card. If they see no route for getting a green card, they will not hire you," explains Shulman. "A lot of companies are afraid of the time and effort."

He advises students to "develop a skill set that is desirable to a company and not held by all others." Only about half of graduates in chemistry do a postdoc, but the additional training is almost mandatory for foreign nationals. During the postdoctoral term, a scientist can acquire additional skills and his or CONTINUED »

- **Association of American Universities** http://www.aau.edu
- **Cold Spring Harbor Laboratory** http://www.cshl.edu
- **Division of International Services/ ORS, NIH** http://www.ors.od.nih.gov
- **McGill University** http://www.mcgill.ca
- **The National Academies** http://www.nas.edu
- **University of Cincinnati** http://www.uc.edu
- **University of Michigan** http://www.umich.edu

UNIVERSITY OF ALBERTA
EDMONTON, ALBERTA, CANADA

www.careers.ualberta.ca

Assistant or Associate Professor in Neurobiology

We invite applications for a tenure-track position at the Assistant or Associate Professor level in research areas related to comparative neurophysiology, neuropathogenesis or molecular neurobiology. The successful candidate will be expected to interact with a strong comparative physiology group that has expertise in developmental, molecular and evolutionary neurophysiology, and cellular neuroendocrinology. Strong collaborative interactions are also available with the Centre for Neurosciences and the Centre for Prions and Protein Folding Diseases. The candidate should have a strong record of research and demonstrated potential for excellence in teaching. The University of Alberta offers a competitive salary commensurate with experience and an excellent benefits plan.

The Department of Biological Sciences (http://www.biology.ualberta.ca/), with 72 faculty members and 275 graduate students, offers an exciting environment for collaborative research. Exceptional infrastructure includes molecular biology and microscopy/imaging services, animal care and aquatic facilities and access to Bamfield Marine Sciences Centre.

Candidates should submit a curriculum vitae, a one-page summary of research plans, a statement of teaching interests and reprints of their three most significant publications preferably electronically to positions@biology.ualberta.ca or to:

Dr. L. S. Frost, Chair
Department of Biological Sciences
CW 405 Biological Sciences Building
University of Alberta
Edmonton, Alberta, Canada T6G 2E9

Applicants must also arrange for three letters of reference to be sent to the Chair. Closing date for this position is April 1, 2007. The effective date of employment will be January 1, 2008.

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. If suitable Canadian citizens and permanent residents cannot be found, other individuals will be considered. The University of Alberta hires on the basis of merit. We are committed to the principle of equity in employment. We welcome diversity and encourage applications from all qualified women and men, including persons with disabilities, members of visible minorities, and Aboriginal persons.

CARDIOVASCULAR GENOMICS DIRECTOR
CENTER FOR TRANSLATIONAL MEDICINE
Jefferson Medical College, Philadelphia, Pennsylvania

The Center for Translational Medicine in the Department of Medicine, Jefferson Medical College seeks an outstanding scientist for establishment of a program in cardiovascular genomics or pharmacogenomics and heading a Core unit within the Center and Department. A tenure-track appointment is available at any level depending on qualifications and experience. We seek a scientist who will complement and synergize with ongoing basic and clinical research programs in the Department of Medicine and within Thomas Jefferson University. In particular, we seek individuals with research interests in cardiovascular genomics/genetics with experience in the latest technology and bioinformatics and who can not only direct their own research program but also head an existing Genomics Core. The multidisciplinary Center has state-of-the-art technology in gene discovery, gene and cell transfer, imaging, functional genomics and animal models of human disease and is housed within a new 30,000 sq ft facility. In addition, collaborative opportunities are available in the Cardeza Foundation for Hematologic Research, the Kimmel Cancer Center, the Vascular Center, and a newly established Center for Kidney disease.

Interested candidates should have an MD, PhD or MD/PhD degree and a strong academic record. Candidates with extramural support will be a priority but not a requirement, however, young investigators must have excellent training and track record. Competitive packages will be offered based on qualifications. Located in Center City Philadelphia, Jefferson Medical College is one of the oldest and highly respected medical schools in the U.S. Founded in 1824, the Medical College is part of Thomas Jefferson University and affiliated with Thomas Jefferson University Hospital and the Jefferson Hospital for Neurosciences.

Please send letters of interest and CV's to: **Walter J. Koch, PhD, Director, c/o Ms. Margit Neszmelyi, Center for Translational Medicine, Jefferson Medical College, 1025 Walnut Street, Room 317, Philadelphia PA 19107; Email: Margit.Neszmelyi@Jefferson.edu; Ph: 215-955-9982.**

Faculty Recruiting in Cancer Research

The Jackson Laboratory

The Jackson Laboratory, a world-renowned mammalian genetics research institution and NCI-designated Cancer Center, has launched a major faculty expansion in Cancer Research.

We encourage applications for positions at the Assistant, Associate and Full Professor level, especially from those with an interest in interdisciplinary and/or translational approaches. Candidates should have a Ph.D., M.D., or D.V.M., and have completed postdoctoral training with a record of research excellence, and they must have the ability to develop a competitive, independently-funded research program that takes advantage of the mouse as a genetic model for human cancer.

We offer a unique scientific research environment, including excellent collaborative opportunities within our faculty of 37 principal investigators, unparalleled mouse genomic resources, outstanding core scientific support services, highly successful postdoctoral and predoctoral training programs, and a major scientific meeting center, featuring courses and conferences centered on mouse models.

For more information go to: www.jax.org

Applicants should send a curriculum vitae and a concise statement of research interests and plans, and arrange to have three letters of reference sent to: facultyjobs@jax.org
The Jackson Laboratory is an EOE/AA employer.

The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609

www.jax.org

her publications have time to accrue citations, one of the criteria for obtaining a green card via the "outstanding researcher" application route. "You have to somehow lower the activation barrier," says Shulman.

Learning the Talk...

When **Xinyan Huang** left China to pursue graduate studies at the University of Toledo, Ohio, spoken language was a major obstacle. Although she practiced long hours to prepare for her graduate school interview and was able to introduce herself to her committee, she did not understand many of the questions they asked.

Like Huang, most foreign scientists in the United States come from China and, for most of them, language is often an issue. So much so that Jim Samet and Chinese-speaking colleagues at the U.S. Environmental Protection Agency decided to write a guide, *The Illustrated Chinese-English Guide for Biomedical Scientists*, to "help build confidence in the use of scientific English," says **John Inglis**, director of Cold Spring Harbor Press, publisher of the book. The guide provides lists of terms that are common in science laboratories translated in both simplified and complex English. The accompanying "talking" website (http://chinese-english.cshl.org) gives the correct pronunciation of these terms.

Language problems can of course be overcome with time and practice. Huang, who has been a postdoctoral fellow in Richard Neubig's lab at the University of Michigan since 2002, says she no longer finds it difficult to be understood, but writing grants and manuscripts is still a challenge. Having completed nearly five years of postdoctoral training, Huang has thought of moving back to China. "Recently a colleague returned [to China] and obtained a good startup position. If I went back I would have a good opportunity," says Huang. "But my passion for science and doing cutting-edge work keeps me here." Huang is optimistic that she will be able to obtain a position as an independent investigator in the United States, although she is not quite ready to take the plunge. "At least for now, my plan is to publish more papers, get a career transitional award, and look for a faculty position soon," she says.

...And Walking the Walk

Seattle-based author **Kathy Barker,** whose books *At the Bench* and *At the Helm* provide practical advice for working in and running a scientific lab, often receives questions from foreign-language scientists. "A lot of the things that I write about in *At the Bench* that are pretty common sense to U.S. scientists are not common sense to [foreign-born ones]. For example they don't know that they can talk to their department chair or that they can call the grant officer at NIH," says Barker. "The non-English speakers especially have trouble understanding the institutional goings-on."

Many foreign scientists seek out support groups of other foreign-born scientists who can help them navigate the system." I know about 40 Chinese colleagues in the U.S. and we call each other to exchange information," says Huang. "The challenge foreign scientists have is to find a support network. But nowadays, thanks to the Internet, a lot of connections are done before they even get in the country," says **Calendario Zapata,** director for the Division of International Services at NIH. Although his office's primary role is to provide foreign scientists employed at the National Institutes of Health in Bethesda, Maryland, help with their immigration papers, it provides other types of information, from filing income taxes to finding local child care.

"My passion for science and doing cutting-edge work keeps me here," says Xinyan Huang.

The National Postdoctoral Association (NPA) (http://www.nationalpostdoc.org) has put together a guide to help newcomers. "The impetus for the project was a workshop at one of the NPA's annual meetings where postdocs brought up many common and practical questions," says Gamberi, who is now a staff scientist at McGill University in Montreal, Canada. One of the main resources in the guide is information about different types of visas. Obtaining permanent residence in the United States requires a lengthy process. Thus, most foreign scientists coming to the United States initially apply for temporary visas. Once they are in the country, they can often apply for a more permanent status. The most common types of visas sought by scientists are: F-1, usually for undergraduate and graduate students at universities; H1-B, for temporary workers in specialty occupations; and J-1, for exchange visitors. Although most institutions provide help with obtaining a visa, they don't always point out the advantages of one visa type over the other. "One can be more restricted than the other depending on your career path," explains Gamberi.

Foreign scientists not only have to learn how to navigate the U.S. system to advance in their careers, but also adjust to all the practical aspects of daily life in the United States. "Benefits have to be discussed in the U.S. In Europe you just have them," says Gamberi. Other things that a foreigner has to learn are how to obtain a credit card and to build up a credit history. Indeed the biggest challenges for Lazebnik were things like obtaining a checkbook. "I had never seen a checkbook before coming to America. In Russia we just used cash at that time," he recalls. His supervisor assigned another postdoc in the lab with the task of taking Lazebnik to look for apartments, find a bank, and just explain how things worked. That was a huge help to Lazebnik, and he still remains grateful to the former labmate, Alastair MacKay, and within a month he was more or less settled.

For years the United States has attracted the best scientists from around the world. While many return to their countries of origin to share their acquired experience and knowledge, some have made the United States their permanent home despite the challenges facing them and have built successful careers. Continuing to lure top international scientists to the United States will benefit research both locally and worldwide, to the overall benefit of the global scientific endeavor.

» Visit www.sciencecareers.org and plan to attend upcoming meetings and job fairs that will help further your career.

Laura Bonetta is a scientist turned freelance writer based in the Washington, D.C. area. She has a green card.

POSITIONS OPEN

MICROBIOLOGIST
University of North Texas, Denton, Texas

The Department of Biological Sciences **(website: http://www.biol.unt.edu)** invites applications for a tenure-track **ASSISTANT/ASSOCIATE PROFESSOR** in microbiology beginning September 2007. Successful candidates will be expected to contribute to a strong research program and participate in instruction at the undergraduate and graduate levels. Candidates able to apply modern genomic methods to research on the physiology and diversity of microorganisms are strongly encouraged to apply, but candidates with expertise in other areas will also be seriously considered. Excellent opportunities to interact with research faculty in the areas of biochemistry, microbiology, biotechnology, plant, and environmental sciences exist.

University of North Texas is a growing University of over 33,000 students located in the Dallas-Fort Worth metroplex. Degree programs are offered in biology, biochemistry, molecular biology, and environmental sciences at both the undergraduate and graduate (M.S./Ph.D.) levels. Excellent research facilities, competitive salary, and generous startup funds are available. Submit curriculum vitae, names of three references, reprints, and statement of research goals to: **Dr. Daniel Kunz, Search Committee Chair, Department of Biological Sciences, P. O. Box 305220, University of North Texas, Denton, TX 76203-5220.** Review of applications will begin February 16, 2007, and will remain open until filled.

The University of North Texas is an Equal Opportunity Affirmative Action Institution committed to diversity in its employment and educational programs, thereby creating a welcoming environment for everyone.

ASSISTANT or ASSOCIATE PROFESSOR
Department of Cell Biology and Anatomy
Louisiana State University
Health Sciences Center, New Orleans

The Department of Cell Biology and Anatomy **(website: http://www.medschool.lsuhsc.edu/cell_biology/)** invites applications for a tenure-track faculty position at the Assistant or Associate Professor level. We are seeking individuals with research interests in any aspect of developmental biology, including developmental neuroscience. Applicants should have an independent, well-funded research program and be willing to participate in teaching medical and graduate student courses. To apply, please send curriculum vitae, statement of research interests, and the names of three references to: **Melissa Hebert, Department of Cell Biology and Anatomy, Louisiana State University Health Sciences Center, 1901 Perdido Street Box P6-2, New Orleans, LA 70112-1393.** *Louisiana State University Health Sciences Center is an Equal Opportunity/Affirmative Action Employer.*

The Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, announces the availability of a **TENURE-TRACK FACULTY** position (open rank) in the area of cardiovascular/endocrine research, a growing focus in our Department. A strong research program and evidence of a commitment to excellence in teaching are required. Departmental faculty and their interests can be identified at **website: http://www.cvm.tamu.edu/vtpp.** Evaluation of applications will begin March 1, 2007, and continue until the position is filled. Candidates should send curriculum vitae, letter of application, and names and addresses of three references to:

Dr. Timothy A. Cudd,
Department of Veterinary Physiology and Pharmacology, Texas A&M University
College Station, TX 77843-4466
Telephone: 979-862-1972
Fax: 979-845-6544, e-mail: tcudd@cvm.tamu.edu

Texas A&M University is an Equal Opportunity Employer/Educator.

POSITIONS OPEN

The University of Alabama at Birmingham seeks applications for up to two full-time **ASSISTANT PROFESSOR** positions in the Department of Anesthesiology. These are tenure-earning track positions and intended to attract highly qualified candidates, with a demonstrated track record in lung electrophysiology, willing to function as independent investigators, while at the same time, collaborate with other faculty members in a number of collaborative projects. The successful candidates must have considerable expertise with cell and molecular aspects of ion transport, including whole and single channel currents recordings from oocytes and mammalian cells, as shown by first (or senior) author publications in high impact peer-reviewed journal. Candidates must have current extramural funding from a national agency and show outstanding potential for obtaining NIH Research Project Grant funding. Outstanding teaching credentials are highly desirable. Prospective candidates should hold a Ph.D. and/or M.D. degree. Please send curriculum vitae to: **Sadis Matalon, Ph.D., Alice McNeal Professor of Anesthesiology, Professor of Physiology and Biophysics, Microbiology and Environmental Health Sciences, Department of Anesthesiology, The University of Alabama at Birmingham, Biomedical Research Building II – Room 224, 901 19th Street South, Birmingham, AL 35294-2180, fax: 205-934-7476, e-mail: sadis@uab.edu.** *The University of Alabama at Birmingham is an Equal Opportunity, Affirmative Action Employer with a strong commitment to ethnic and cultural diversity among its faculty, students, and administrative staff. Applications from women and ethnic minorities are encouraged.*

BIOCHEMISTRY, TENURE-TRACK FACULTY POSITION, Department of Chemistry and Molecular Biology, North Dakota State University (NDSU) has a tenure-track faculty position available August 2007.

Ph.D. in biochemistry, chemistry, or molecular biology required. Postdoctoral experience preferred. Applicants having research interests in the areas of forensic DNA and molecular biology which are related to National Institute of Justice-targeted funding priorities will be given preference. The successful candidate will be encouraged to work closely with the staff of the newly created NDSU Forensic DNA Facility. Teaching duties may include introductory biochemistry courses at the undergraduate or graduate levels and a graduate course related to specialty area. Must have the potential to develop an externally funded, competitive research program and commitment to teaching and service. The position is open at the rank of **ASSISTANT** or **ASSOCIATE PROFESSOR.** Screening will begin March 1, 2007. For further information and application requirements see **website: http://www.ndsu.edu/ndsu/jobs/non_broadbanded/positions/00025232.shtml.** Contact person: **Dr. S. Derek Killilea, Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, ND 58105. Telephone: 701-231-7946, fax: 701-231-8324.**

NDSU is an Equal Opportunity Institution.

NATIONAL UNIVERSITY OF SINGAPORE
Department of Chemical and Biomolecular Engineering

The Department of Chemical and Biomolecular Engineering at National University of Singapore invites applications for **TENURE-TRACK FACULTY** positions at all levels. The Department is one of the largest internationally with excellent in-house infrastructure for experimental and computational research. A Ph.D. in chemical engineering or related areas and a strong research record with excellent publications are required. Please refer to **website: http://www.chbe.nus.edu.sg/** for more information on the areas of interest and for application details. Applicants should send full curriculum vitae (including key publications), a detailed research plan, a statement of teaching interest, and a list of names of at least three references to: **Professor Raj Rajagopalan, Head of Department (Attention: Ms. Nancy Chia, e-mail: nancychia@nus.edu.sg).**

POSITIONS OPEN

BIOLOGY EDUCATOR
ASSISTANT PROFESSOR

The Biological Sciences Department at California State Polytechnic University, Pomona, invites applications for a tenure-track position in biological education at the rank of Assistant Professor to begin September 2007. The new faculty member will teach classes in science/content methods leading to the teaching credential, develop specialty courses and workshops for science teachers, and will be expected to establish and maintain an externally funded research program in science education involving undergraduate and Master's level students. The successful candidate will also be expected to assist in curriculum development, advise students, serve on Department, College, and University committees, and engage in professional activities. Ph. D. required from an accredited institution by August 2007, a combination of graduate degree and/or work experience in both biology and science education, and possess or be qualified to obtain a California teaching credential in a single subject area. Application review will begin March 1, 2007, and will continue until position is filled.

Address all nominations, inquiries, and requests to:

Dr. Gil Brum and Tina Hartney
Co-Chairs, Biology Educator Search Committee
Biological Sciences Department
California State Polytechnic University, Pomona
3801 West Temple Avenue
Pomona, CA 91768
Telephone: 909-869-4036, fax: 909-869-4078
E-mail: gdbrum@csupomona.edu

FACULTY POSITIONS IN PHARMACEUTICS AND DRUG DELIVERY
Department of Pharmaceutical and Biomedical Sciences
College of Pharmacy, University of Georgia

The Department of Pharmaceutical and Biomedical Sciences at the University of Georgia, Athens, invites applications for a tenure-track **ASSISTANT PROFESSOR** position in the general area of drug delivery and drug transport. Applicants should possess a Ph.D. or Pharm.D./Ph.D. or equivalent degree with pharmaceutical sciences or a related area as the focus of their graduate education and research training. Excellent communication skills and the ability to teach basic pharmaceutics and drug delivery concepts at both the Pharm.D. and Ph.D. levels are required. Each successful applicant is expected to develop a dynamic, extramurally funded research program in the area identified above. To be assured of full consideration, applications should be received by March 1, 2007. Interested qualified applicants should submit a letter of application, curriculum vitae, a research plan, and three confidential letters of recommendation to: **Chair, Pharmaceutics Search Committee, Department of Pharmaceutical and Biomedical Sciences, R.C. Wilson Pharmacy Building, University of Georgia, Athens, GA 30602-2352.** Applicants may also apply online to **e-mail: pbssearch@rx.uga.edu.** *The University of Georgia is an Equal Employment Opportunity/Affirmative Action Employer. Applications from qualified women and minority candidates are encouraged.*

Virginia Tech is recruiting the **FOUNDING DIRECTOR** for the Institute of Biomedical and Public Health Sciences (IBPHS), **website: http://www.ibphs.vt.edu.** IBPHS is a major initiative at Virginia Tech to enhance research and training in the life sciences. The successful candidate will have a vision to use interdisciplinary biomedical and public health research to address significant societal needs and to compete for major federal and private funding; will maintain a productive, internationally recognized research program; and will be a spokesperson for the Institute within the University and with external constituents. For detailed information and instructions on how to apply see **website: http://www.jobs.vt.edu** and search for posting 061454. *Equal Opportunity/Affirmative Action.*

UK
UNIVERSITY OF KENTUCKY
College of Medicine

Faculty Position

The University of Kentucky's Sanders-Brown Center on Aging is seeking a **neuroepidemiologist, neuropsychologist, neurologist,** or **psychiatrist** with an interest in research in Alzheimer's disease. This individual would be expected to function in the Clinical Core of the NIH-funded UK Alzheimer's Disease Center and establish a research program utilizing the Clinical, Neuropathology, and Biostatistical and Data Management Cores facilities and data. The candidate will join a large team of clinical and basic science investigators studying Alzheimer's disease. This is a tenure track faculty position at the Assistant or Associate Professor level. Preference will be given to individuals with research experience and accomplishments. Faculty rank will be commensurate with experience and qualifications. Minimal teaching and service obligations are required.

Applicants should send a letter of interest, CV, and names of three references to: **William R. Markesbery, M.D., Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536-0230**.

The University of Kentucky is an Equal Employment Opportunity/Affirmative Action Institution. If offered this position, you will be required to pass a pre-employment drug screen and undergo a national background check as required by University of Kentucky Human Resources.

VCU

Virginia Commonwealth University

TENURE-TRACK FACULTY POSITIONS

Chemical and Life Science Engineering

The Department of Chemical and Life Science Engineering (CLSE) in the School of Engineering at Virginia Commonwealth University (VCU) has two tenure-track faculty openings starting in the Fall of 2007. One position is at the **Associate level**, and the other is at the **Assistant level**.

Chemical and Life Science Engineering at VCU represents the broad, formal interaction of the disciplines of chemical engineering with life and health sciences to create a forward-looking, nationally distinct program. Many of the Life Science areas at VCU enjoy national rankings, including those in the medical sciences, biological sciences and environmental life sciences. The new School of Engineering formed in 1996 has embarked on a "25 in 25" initiative to become a top 25 program in 25 years. Notable facilities include the new 120,000 sq ft School of Engineering building, the new Trani Center for Life Sciences, the Rice Institute for Environmental Life Sciences located along the coastal plain region of the James River, and VCU's Medical School and Hospitals. Current research areas in CLSE include stem cell and stem-cell derived tissue engineering, cellular engineering and signal pathway analysis, biological systems engineering, bioinformatics and biocomputing, genetic and protein molecular engineering, small molecule and cellular based therapeutics, reaction engineering and molecular transport, advanced polymeric materials and processing methods. A new research Institute for Health and Life Science Engineering and a new Phase II Engineering building expansion will be open in 2007-2008 that will greatly expand and enhance research and education capabilities in the life science engineering areas.

Candidates must have earned a Ph.D. and at least one degree in Chemical Engineering or Bioengineering or closely related discipline.

Outstanding candidates should submit a complete curriculum vitae, statement of research and teaching interests, and a list of four references to: **Dr. Michael H. Peters, Chair, Chemical and Life Science Engineering, Virginia Commonwealth University, 601 West Main St., Room 403A, P.O. Box 843028, Richmond, VA 23284-3028.**

Electronic submissions are acceptable by *.pdf files only please to: **jbschrei@vcu.edu.** Candidates must be eligible for employment in the United States by indicating their citizenship or visa status. Review of applications will continue until the positions are filled.

Virginia Commonwealth University is an Equal Opportunity, Affirmative Action Employer. Women, minorities and persons with disabilities are encouraged to apply..

Mathematics and Computational Biology Position at Vanderbilt University Medical Center

Senior Scientific Data Analyst: The position requires an advanced degree with a minimum of 36 months experience in data analysis, mathematics or statistics. Applicant should have experience in statistical analysis of complex data sets, sample size calculations, and clustering. Experience in developing computer programs for analysis of large data sets and informatics are advantages. You must be well organized, efficient, and able to design scientific experiments. The successful applicant will work as part of an interdisciplinary group on analysis of mass spectrometry based lipid profiling of cellular signaling and metabolic pathways. Some experience in mathematical modeling is desirable.

Position title, salary, and specific responsibilities can be adapted to degree and previous experience. The position can be classified as a Research Assistant Professor or Senior Staff Scientist position for someone with a Ph.D. and extensive publications, or a Research Specialist for an M.S.

Interested applicants should send CV, contact information for three references to:

H. Alex Brown
Ingram Professor of Cancer Research
Department of Pharmacology: 442 RRB
Vanderbilt University School of Medicine
23rd Ave South & Pierce
Nashville, TN 37232-6600
alex.brown@vanderbilt.edu

LSU Health Sciences Center
NEW ORLEANS

Professor and Head
Department of Pharmacology

Louisiana State University Health Sciences Center, School of Medicine, New Orleans

The Louisiana State University Health Sciences Center School of Medicine in New Orleans invites applications and nominations for Professor and Head of the Department of Pharmacology. The School is renewing a period of extraordinary expansion with unprecedented investments by the state of Louisiana in the further development of biomedical sciences in collaborations between the School of Medicine and internal and external agencies. The position presents the opportunity to create a new level of interdisciplinary research and collaboration in a department with complementary and diverse areas of expertise that include cardiovascular, CNS, respiratory and gastrointestinal pharmacology, drug metabolism, and cellular and molecular signaling. The Department currently lists 24 full time faculty, 5 faculty with adjunct appointments, and 17 students in Ph.D. or M.D./Ph.D. programs. Many of the full-time faculty members hold joint appointments in the Cancer Center, Neuroscience Center of Excellence, Cardiovascular Center, Alcohol Research Center and Center for Oral and Craniofacial Biology. The Department participates in Interdisciplinary and Departmental graduate programs leading to a doctorate in Pharmacology. The Department also currently holds an NIH COBRE grant, "Mentoring in Cardiovascular Biology," to train junior faculty. The successful candidate will have a Ph.D. and/or M.D. degree, demonstrable leadership ability, a well-funded and internationally recognized research program, a proven commitment to education and research, and the ability to provide vision for the Department that builds on its historic strengths. Achievements in teaching, multi-disciplinary collaborative research, mentorship, and administration that promote an inclusive environment are essential. Additional information regarding the Department and Health Sciences Center can be obtained at **http://www.medschool.lsuhsc.edu/pharmacology/**.

Candidates should provide a *curriculum vitae* including a full list of publications, past and current research support, and a brief statement of educational, research, service, and administrative interests. These materials should be forwarded electronically to: **Dr. Arthur L. Haas, Chair, Pharmacology Search Committee, LSUHSC School of Medicine, Department of Biochemistry, 1901 Perdido Street, New Orleans, LA 70112; PharmacologySearch@lsuhsc.edu.** Review of applications will commence **1 March 2007** and will continue until the position is filled.

LSUHSC is an Equal Opportunity/Affirmative Action Employer.

The **University of California, Davis**, invites applications for an **Assistant Professor** position. This position will be housed in the **Department of Plant Sciences** with the possibility of a joint appointment in the Department of Viticulture and Enology, if appropriate. A demonstrated capacity to conduct high quality research and ability to teach undergraduate and graduate students are requirements. The successful candidate's research will focus on understanding the biochemical pathways leading to the production and accumulation in plants and plant products of various compounds important for human health (phytonutrients) and using this information to enable fundamental human nutritional insights and to direct crop improvement. The range of potentially important phytonutrients for human health is quite broad and includes: polysaccharides; isoprenoids and their derivatives including carotenoids, vitamin E, and sesquiterpenes; phenylpropanoids including flavonoids, isoflavanoids and other polyphenolics; and various bio-active alkaloids and peptides.

This position is an integral part of the UC Davis campus-wide initiative on Foods for Health and the successful candidate will be expected to operate well in a multi-disciplinary team focused on the development of a comprehensive program that covers the entire continuum of food production, consumption and individualized health. A Ph.D. and postdoctoral research experience in plant biochemistry or a related field is required and specific experience in studying the biosynthesis and/or human nutritional impact of phytonutrients is desirable. The position will be at the Assistant Professor level, and will be an academic year (9 month) tenure track position; a fiscal-year term appointment (11 months) will be offered and continued based on academic personnel review.

Please refer to **http://plantsciences.recruitments.ucdavis.edu** for position details and online application process. Please include statements of research and teaching interests, curriculum vitae, publication list, copies of 3 of your most important research publications, copies of undergraduate and graduate transcripts (if within 5 years of either degree), and the names, e-mail addresses, and telephone numbers of at least five professional references. For technical or administrative questions regarding the application process please email **plantsciences@ucdavis.edu**. For inquiries regarding the position please contact **Dr. Alan Bennett**, Chair of the search committee (**abbennett@ucdavis.edu**). Review of the applications will begin **March 31, 2007**. The position will remain open until filled.

The University of California is an Affirmative Action/ Equal Opportunity Employer.

University of Nebraska Medical Center Department of Genetics, Cell Biology and Anatomy

DEVELOPMENTAL GENETICS / BIOLOGY
REGENERATIVE MEDICINE
CANCER GENETICS / BIOLOGY

Applications are invited from established investigators (any academic rank) or multi-investigator teams working in one or more of the areas indicated above. The individuals recruited to these tenure eligible positions will be expected to maintain an independent, extramurally funded, research program, contribute to one or more collaborative research programs within our medical center and participate in the educational programs of the University. Research areas of interest include, but are not limited to, development and/or cancer of the hematopoietic system, breast, lung, liver, kidney, GI tract and retina. Outstanding start-up resources, laboratory facilities and shared laboratory resources are available. Omaha, the nation's 42nd largest city, offers an outstanding school system, moderate cost of living, and numerous cultural and recreational activities.

Applicants with a Ph.D., M.D., or other doctoral degree and a clear record of research accomplishments are invited to submit their curriculum vitae, a concise summary of their ongoing/future research and the names of three or more qualified references to: **Dr. James Shull, Chairman, Department of Genetics, Cell Biology and Anatomy, University of Nebraska Medical Center, 985805 Nebraska Medical Center, Omaha, NE 68198-5805**. Review of applications will begin **March 15, 2007** and will continue until the positions are filled.

The University of Nebraska is an Equal Opportunity/Affirmative Action Employer. Individuals of culturally diverse backgrounds and women are encouraged to apply.

http://www.unmc.edu/genetics

Sigfried and Janet Weis Center for Research
Geisinger Clinic
SCIENTIST FACULTY

The Weis Center for Research is seeking outstanding independent scientists for full time positions at ranks equivalent to Assistant, Associate or Full Professor at academic institutions. Candidates should have proven records of accomplishment in conducting innovative research at the molecular, cellular or genetic level in areas relevant to human disease. Applicants should have a Ph.D. and/or M.D. degree and three or more years of postdoctoral training. Candidates for senior positions are expected to have a significant history of extramural funding. The Weis Center is located on the campus of the Geisinger Medical Center, which is situated in an attractive semi-rural community that affords an outstanding quality of life plus convenient access to major metropolitan areas. Substantial resources are available for start-up, ongoing research support and salary. More information about the research, core facilities, and faculty at the Weis Center for Research can be found at **http://www.geisinger.org/professionals/research/wcr**.

Qualified individuals should submit curriculum vitae, statement of research interests and three reference letters to: **Ms. Kristin Gaul (DJC), Weis Center for Research, Geisinger Clinic, 100 North Academy Avenue, Danville, PA 17822-2600**; or submit via email to **kgaul@geisinger.edu**. Please refer to position **WCR-010228** in the subject line. Applications will be accepted until the position is filled.

Affirmative Action/Equal Opportunity Employer.

Geisinger Health System

Heal. Teach. Discover. Serve.
www.geisinger.org

Professor and Chair Department of Physiology

New York Medical College, located in Valhalla, New York is seeking a nationally recognized academic leader to Chair the Department of Physiology. The candidate should have a Ph.D. or M.D. and be an internationally recognized scientist with an outstanding funded research program and a distinguished academic record. The candidate should have a record of strong academic leadership in the areas of undergraduate medical education and basic science graduate programs; and have demonstrated ability to enhance research programs and foster a scholarly environment. Internal candidates will also be considered.

Please send letters of application and curriculum vitae or nominations preferably electronically, by March 15 to:

teresa_longhitano@nymc.edu *or*

Search Committee for Chair of Physiology
c/o Office of the Provost & Dean
New York Medical College
Administration Building Room 109
Valhalla, NY 10595
Tel (914) 594-4900 • Fax (914) 594-4145

Equal Opportunity Employer

MAYO CLINIC

Faculty Position in Cancer Pharmacology

The Division of Oncology Research and the Department of Molecular Pharmacology and Experimental Therapeutics of the Mayo Clinic College of Medicine seek an outstanding research investigator in the area of cancer pharmacology. Research within the Division is highlighted at **http://cancercenter.mayo.edu/mayo/research/developmental_therapeutics/**.

Applications for either an Assistant Professor or more senior level appointment are welcomed. Investigators with expertise in the areas of proliferative signaling, cell cycle checkpoints, DNA repair, cancer pharmacogenomics and/or rational drug design are particularly encouraged to apply.

A curriculum vitae, selected publications, and a statement of research interests, should be submitted by **March 31, 2007** to:
Deb Strauss (strauss.debra@mayo.edu)
or to:
Scott Kaufmann, M.D., Ph.D.
Search Committee Chair
Guggenheim 1301
Mayo Clinic
Rochester, MN 55905

UNIVERSITY OF ALBERTA
EDMONTON, ALBERTA, CANADA

www.careers.ualberta.ca

Assistant Professor, Pediatric Surgery

The Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine and Dentistry at the University of Alberta, Canada, invites applications for a contingent faculty position. We primarily seek candidates at the Assistant Professor level, but exceptional candidates at a more senior level will be considered. We seek an individual who will complement and extend our existing strengths in cell signaling/cell cycle, protein targeting, organelle biogenesis, cell-cell interaction, neurobiology and RNA localization. We are particularly interested in individuals who investigate questions of musculoskeletal growth and development particularly with respect to the spine, although applicants in all areas of modern cell biology related to growth and development will be considered. Applicants should have a PhD, a proven record of research achievement and will be expected to apply for funding from the Alberta Heritage Foundation for Medical Research or other granting agencies. The successful candidate will conduct a research program in collaboration with a multidisciplinary research group at the University of Alberta. A contribution to the Department's teaching program will also be expected.

Please send a curriculum vitae, a two-page statement of research interests, and arrange to have three letters of reference sent on your behalf to:

Dr. Douglas Hedden
Chair, Department of Surgery
University of Alberta
Edmonton, Alberta, Canada T6G 2B7

Consideration of applications will begin on April 30, 2007 and will continue until the position is filled.

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. If suitable Canadian citizens and permanent residents cannot be found, other individuals will be considered. The University of Alberta hires on the basis of merit. We are committed to the principle of equity in employment. We welcome diversity and encourage applications from all qualified women and men, including persons with disabilities, members of visible minorities, and Aboriginal persons.

MGH 1811

MASSACHUSETTS GENERAL HOSPITAL HARVARD STEM CELL INSTITUTE

The Center for Regenerative Medicine (CRM) at Massachusetts General Hospital invites applications for a tenure-track assistant professor position. Outstanding scientists in the field of stem cell biology who have the demonstrated ability to develop a strong independent research program will be considered. Successful candidate(s) will be members of the **Harvard Stem Cell Institute** and faculty of Harvard University. Candidates must hold a PhD and/or MD and have a history of innovative, interactive research. Women and minority candidates are urged to apply.

Applicants should send an electronic copy of (1) letter of interest (2) research plan and (3) current curriculum vitae to **Dr. David Scadden c/o Chris Shambaugh: cpasker@partners.org**. Three letters of recommendation should also be sent directly to:

Center for Regenerative Medicine Search Committee
Attention: Chris Shambaugh
Massachusetts General Hospital
185 Cambridge St.
CPZN 4265A
Boston, MA 02114

MGH is an Equal Opportunity/Affirmative Action Employer.

Faculty Positions
Department of Pharmacology
The University of Michigan

The Department of Pharmacology is seeking applications for tenure-track positions at the **ASSISTANT**, **ASSOCIATE** or **PROFESSOR** level. We are seeking outstanding individuals with research experience and interests that augment current department initiatives in *Drug Metabolism, Pharmacogenetics, Clinical Pharmacology, and Signal Transduction, Neuropharmacology/Behavioral Pharmacology.* Qualifications include a Ph.D. in Pharmacology or a related discipline and/or M.D. degree, 3-5 years of postdoctoral experience, and research accomplishments as evidenced by scholarly contributions to the literature.

For the Drug Metabolism position, applicants with outstanding backgrounds in Phase I/Phase II drug metabolism are encouraged. For the Pharmacogenetics position, consideration will be given to applicants with experience in the identification and characterization of polymorphic genes encoding xenobiotic metabolizing enzymes/transporters or involved in their regulation in animals or humans. Clinical Pharmacology candidates with experience in drug metabolism and/or pharmacogenetics are welcome. Signal transduction and neuropharmacology/behavioral pharmacology candidates studying molecular to whole animal aspects of pharmacology/drug design are encouraged to apply.

Successful candidates will be expected to establish an externally funded research program and to participate in teaching medical students and other health professionals, as well as graduate and postdoctoral students. An attractive startup package including excellent laboratory facilities and generous startup funds will be available.

Information about current faculty interests is available at **http://sitemaker.umich.edu/pharmacology/faculty_listing**.

Applicants should send their curriculum vitae, a two- to four-page summary of their research program and future research plans, and information related to past and current teaching experience. Three letters of recommendation should also be sent. Address all correspondence to: **Dr. John Traynor, Chair, Pharmacology Search Committee, Department of Pharmacology, The University of Michigan Medical School, 1150 West Medical Center Dr., Ann Arbor, MI 48109-0632**.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer. Applications from qualified women, minorities and/or disabled individuals are encouraged.

URBAN ENVIRONMENT FACULTY POSITION

YALE UNIVERSITY
School of Forestry & Environmental Studies

Yale University's School of Forestry and Environmental Studies (FES) seeks to fill a junior- or senior-level faculty position focused on the urban environment. We seek an individual who takes a quantitative systems approach to urban areas, particularly with a spatial geographical focus. We are particularly interested in an individual concerned with the interface between manmade and environmental systems. Research topics of interest include, but are not limited to, urban land use and land cover; urban modeling, and urban development as they relate to the environment. Interest and experience in international urban systems is desirable. The successful candidate will have an earned doctorate and an active research program that complements those of existing faculty in FES. She or he will demonstrate capacity for excellence in teaching at the graduate level, and will advise Master's and Doctoral students. Teaching might include courses that address the environmental aspects of urban land use planning, GIS modeling, transportation analysis and planning, and international urban development. We prefer a candidate with formal training in a relevant discipline such as geography, urban studies, or allied fields. Understanding of key underlying environmental sciences such as ecology or Earth science is desirable.

Applicants should send a c.v., a statement of research and teaching interests, two reprints or other professional publications, and a list of three references to: **Assistant Dean Jane Coppock, Urban Environment Search Committee, School of Forestry and Environmental Studies, Yale University, 205 Prospect St., New Haven, CT 06511, USA**. The deadline for applications is **March 2, 2007**.

Yale University is an Affirmative Action/Equal Opportunity Employer. Men and women of diverse racial/ethnic backgrounds and cultures are encouraged to apply. Women and minority candidates, as well as candidates from developing countries, are particularly urged to apply.

THE UNIVERSITY OF HONG KONG

香 港 大 學

Founded in 1911, The University of Hong Kong is committed to the highest international standards of excellence in teaching and research, and has been at the international forefront of academic scholarship for many years. Of a number of recent indicators of the University's performance, one is its ranking at 33 among the top 200 universities in the world by the UK's Times Higher Education Supplement. The University has a comprehensive range of study programmes and research disciplines, with 20,000 undergraduate and postgraduate students from 50 countries, and a complement of 1,200 academic members of staff, many of whom are internationally renowned.

Temporary Assistant Professor in the Department of Botany
(Ref.: RF-2006/2007-319)

Applications are invited for appointment as temporary Assistant Professor (funded by the Croucher Foundation) in the Department of Botany, from September 2007, on a one-year temporary basis.

Applicants should possess a Ph.D. degree with a strong background and publication record in the field of Plant Molecular Biology and Plant Biotechnology. The appointee is expected to teach courses in Introductory Microbiology, Plant Molecular Biology and Plant Biotechnology, and to participate in research in plant molecular biology. Information about the Department can be obtained at http://www.hku.hk/botany.

Starting annual salary is around HK$451,980 (approximately US$1 = HK$7.8) (subject to review from time to time at the entire discretion of the University). Annual leave and medical/dental benefits will be provided.

Further particulars and application forms (272/302 amended) can be obtained at https://www.hku.hk/apptunit/; or from the Appointments Unit (Senior), Human Resource Section, Registry, The University of Hong Kong, Hong Kong (fax: (852) 2540 6735 or 2559 2058; e-mail: senrappt@hkucc.hku.hk). **Closes April 30, 2007**.

The University is an equal opportunity employer and is committed to a No-Smoking Policy

CASE
CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

Faculty Positions
Department of Pharmacology

Applications are invited from dynamic scientists for several faculty positions in the growing Department of Pharmacology at the Case Western Reserve University School of Medicine. Faculty rank from Instructor to Full Professor is open, dependent on current level of achievement.

The Department has a great tradition of excellence in molecular pharmacology with strong, growing programs in cell regulation and signaling, membrane structural biology, cancer cell biology, and an evolving emphasis on translational pharmacology. The goal of the search is to add to existing strengths in the Department and/or the School of Medicine. The best candidates in any area relevant to modern pharmacology will be competitive. Visit our website **http://pharmacology.case.edu/**.

Applicants should submit a cover letter, their full Curriculum Vitae with publications and grant support, and a list of professional references. In addition, all applications should include descriptions of the applicant's research interests and goals, and teaching, mentoring, and professional service experiences.

Applications should be transmitted by email to **Camala Thompson, (cami@case.edu)**.

In employment, as in education, Case Western Reserve University is committed to Equal Opportunity and World Class Diversity.

The UC Davis Genome Center integrates experimental and computational approaches to address key problems at the forefront of genomics. The Center is housed in a new research building with state-of-the-art computational and laboratory facilities and currently comprises 15 experimental and computation faculty. These faculty are developing an internationally recognized program in genomics and computational biology at Davis, building on and enhancing the unique strengths and unmatched breadth of the life sciences on the UC Davis campus.

The Genome Center invites applications for tenure-track faculty positions in computational and experimental approaches to network and synthetic biology. Candidates may be at any academic level. At the senior level, we invite applications from prominent scientists with distinguished records of research, teaching, and leadership in analysis and manipulation of biological networks. At the junior level, we invite applications from candidates whose accomplishments in innovative research and commitments to teaching demonstrate their potential to develop into the future leaders of these fields.

Candidates should be strongly motivated by the biological importance of their research and should value the opportunity to work in close collaboration with other groups. The Genome Center welcomes applications from strong candidates in all areas of networks and synthetic biology involving medical, animal, plant or microbial systems. Investigators employing large-scale approaches that complement existing strengths at UC Davis are particularly encouraged to apply.

These positions require a Ph.D. or equivalent. These appointments may be at the Assistant, Associate or Full Professor level in an appropriate academic department in any of six schools, or colleges. The position will remain open until filled. For fullest consideration, applicants should submit a letter of application, a curriculum vitae, statements of research and teaching interests, and the names of at least five references to the Genome Center Web site **www.genomecenter.ucdavis.edu** by **March 1, 2007**.

The University of California is an Affirmative Action/Equal Opportunity Employer.

Haskins Laboratories

President and Director of Research

Haskins Laboratories, a private, non-profit research institute in New Haven, CT, devoted to the science of the spoken and written word, is searching for a *President and Director of Research*. The successful candidate should have a Ph.D. in a field related to the research of the Laboratories, experience in extramurally funded research, and be suitable for affiliated academic appointments.

Applicants should send a cover letter, CV, three relevant publications, and a list of three potential references by **March 1, 2007**. Please do not send letters of reference until requested.

Applications should be sent to:
Presidential Search Committee
Haskins Laboratories
300 George Street, Suite 900
New Haven, CT 06511, USA

Haskins Laboratories is an Equal Opportunity Employer.

UNIVERSITY of VIRGINIA HEALTH SYSTEM

Microbial Physiology, Genetics and/or Pathogenesis
Assistant-Associate Professor

The Department of Microbiology at the University of Virginia School of Medicine invites applications for a tenured or tenure-track faculty position at the rank of Assistant or Associate Professor. Candidates should have a Ph.D. or M.D. degree, at least three years of postdoctoral research experience and a commitment to outstanding research and graduate training. The successful candidate will be expected to maintain an energetic and well-funded basic research program in aspects of bacterial physiology, genetics and/or pathogenesis. In addition he/she is expected to actively participate in Department and Medical School teaching. The successful candidate is expected to take a significant role in the continuing development of outstanding basic and clinical research on microorganisms and human disease at the University of Virginia.

The Department of Microbiology offers state of the art research space, numerous core facilities for the support of molecular and cellular research, and a collegial and interactive faculty. Outstanding opportunities exist for collaborative research in both basic and clinical sciences, including programs in microbial pathogenesis, cellular microbiology, infectious diseases and immunology.

Interested applicants should provide a curriculum vita, brief statement of research interests, and arrange to have at least three letters of reference sent to:

Search Committee-Microbial Pathogenesis
Attention: Lynn McCutcheon
Department of Microbiology
University of Virginia Health System
Box 800734
Charlottesville, VA 22908

Fax: (434) 982-1071
Email: lam8t@virginia.edu

Web: http://www.healthsystem.virginia.edu/internet/microbiology/

Review of applications will commence March 1, 2007. The position will remain open until filled.

The University of Virginia is an Equal Opportunity/Affirmative Action Employer.

University of Alabama at Birmingham (UAB)
Chair, Department of Biology
School of Natural Sciences and Mathematics

The UAB School of Natural Sciences and Mathematics (NS&M) invites applications and nominations for the position of Chair of the Department of Biology. The department presently consists of 17 full-time faculty members with over 900 undergraduate majors and nearly 50 MS and PhD students. Departmental strengths include a highly dedicated and collegial faculty with research interests primarily in the ecology, comparative physiology, and molecular biology of aquatic organisms but also in aspects of cancer biology, immunology, and microbiology. A PhD in Biology or related field is required. Candidates must possess a distinguished record of scholarship, a demonstrated commitment to excellence in teaching, outstanding communication and interpersonal skills, and an established record of university and professional service such as to qualify for a tenured Professor position. Applicants should submit a letter of interest summarizing their qualifications, curriculum vitae, statement of vision, other supporting documentation, and contact information for at least five references. Screening will begin in **February 2007** and continue until a suitable candidate has been selected. Please send applications to: **Department of Biology Search Committee, School of Natural Sciences and Mathematics, 1530 3rd Avenue South, CH 464, University of Alabama at Birmingham, Birmingham, AL 35294-1170.** *Women and minorities are strongly encouraged to apply. UAB is an Affirmative Action, Equal-Opportunity Employer.*

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www.uni-frankfurt.de

JOHANN WOLFGANG GOETHE
UNIVERSITÄT
FRANKFURT AM MAIN

Johann Wolfgang Goethe University, Frankfurt am Main, Department of Biochemistry, Chemistry and Pharmacy invites applications for a full-time

Professor (W3) in Inorganic Chemistry

starting as soon as possible. A candidate is sought whose research interests complement the existing expertise of the Institute for Inorganic and Analytical Chemistry. At the same time, current cooperative efforts within the department as well as with the Department of Physics should be strengthened. Active participation in existing research networks (i. e. *Nanonetzwerk Hessen*) as well as collaboration within the framework of new collaborative projects, special research areas (*SFBs*) and excellence clusters are especially important. The research area of suitable candidates should be related to molecular materials (i.e. inorganic/organic hybrid materials, switchable systems, sensors technology). Due to the currently available equipment, an emphasis on surface chemistry would be advantageous.

The designated salary for this position is 'W3' on the German university scale, and facilities (start-up funding, personnel and equipment) will be at 'C4' level. The successful candidate will be required to teach at both Bachelor's and Master's degree level.

The advertised position is subject to the requirements set out in paragraphs § 70 (6) and § 71 of the 'Hessisches Hochschulgesetz'. The successful candidate will be required to participate in the self-government of the University. We are committed to increasing the proportion of female scientific staff at the University and applications from women are especially welcome. Where qualifications are equal, preference will be given to people with disabilities.

To apply, please send a curriculum vitae including your qualifications, accompanied by a letter stating your research and teaching interests to: **The Dean, Department of Biochemistry, Chemistry and Pharmacy, Johann Wolfgang Goethe University, Max-von-Laue-Straße 9, D-60438 Frankfurt am Main, Germany.** The application should arrive not later than **March 5th, 2007**.

Hier wird Wissen Wirklichkeit

University of California
San Francisco

UCSF

A Health Sciences Campus

Assistant/Associate Professor
UCSF Institute for Regeneration Medicine

The Institute for Regeneration Medicine at the University of California, San Francisco is seeking to recruit a new faculty member whose research is focused on stem cell biology and its application. The IRM, headquartered on the Parnassus Campus, is an interactive and collaborative research environment for research spanning basic principles to bedside practice. The Institute emphasizes neuronal, pancreatic, liver, blood, cardiac developmental and stem cell biology to complement strong basic research and clinical programs at UCSF. Members of faculty in this program are expected to further the understanding of stem cell biology and develop better ways to treat and prevent diseases. The successful candidate is expected to have a research plan relevant to stem cell biology, and to be committed to active participation in the affairs of the IRM. The appointee will be a member of the Biomedical Sciences Graduate Program and an appropriate academic department. Candidates are expected to hold a Ph.D. or M.D. degree, and to have demonstrated achievement in their field.

Applicants should submit curriculum vitae, a 1-2 page summary of research accomplishments, 3 letters of reference, a 1-2 page perspective on future research plans, and reprints of major publications. Review will commence by **February 1, 2007**. Please submit curriculum vitae and supporting documents to: **Arnold R. Kriegstein, M.D., Ph.D., Director, UCSF Institute for Regeneration Medicine, Chair, Search Committee, School of Medicine, 513 Parnassus Avenue, Campus Box #0525, San Francisco, CA 94143-0525.**

UCSF is an Affirmative Action/Equal Opportunity Employer. The University undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.

PROGRAM HEAD
DEPARTMENT OF MOLECULAR AND CELL BIOLOGY
THE UNIVERSITY OF TEXAS AT DALLAS

The University of Texas at Dallas (UTD) and the School of Natural Sciences and Mathematics (NSM) invites applications and nominations for the position of Head of the Department of Molecular & Cell Biology. An academic appointment at an appropriate level may be part of the position. The department has over 900 undergraduate majors, over 70 graduate students, and focuses on basic research and education at the doctoral and undergraduate levels. Current areas of research include prokaryotic and eukaryotic gene expression, cell biology, neurobiology, bionanotechnology, and structural biology/biophysics. The department has sixteen (16) faculty members and will undergo an extensive expansion over the next five years with a major goal of strengthening interactions with other departments at UTD and other institutes such as U. T. Southwestern Medical School.

We seek an outstanding scientist with strong administrative and leadership abilities, a well- established extramurally funded research program, and a clear vision for the future development of the department. Qualified candidates will hold a Ph.D. or M.D. degree and have a record commensurate with that of a tenured faculty member within the department. We welcome applicants with research expertise in any area of contemporary molecular and cell biology; candidates with strong interdisciplinary research programs are particularly encouraged to apply. The successful candidate will be offered an attractive package of resources including research space in the new Natural Sciences and Engineering Research Laboratory, a 190,000 sq. ft., state-of-the-art facility developed to foster interdisciplinary research.

For more information, see the website: **http://www.utdallas.edu/biology**. Applications will be accepted until **April 15, 2007**. Applicants should send curriculum vitae, a short description of research plans, a concise statement of leadership philosophy, and names and contact details of five references to: **Academic Search #2086, The University of Texas at Dallas, P. O. Box 830688—AD 42, Richardson, TX 75083-0688**. Indication of sex and ethnicity for affirmative action statistical purposes is requested as part of the application but not required.

UTD is an AA/EO university and strongly encourages applications from candidates who would enhance the diversity of the university's faculty and administration.

Chair, Department of Physiology
Morehouse School of Medicine

The Morehouse School of Medicine is seeking a Chair for its Department of Physiology. The successful candidate will be an outstanding nationally recognized scientist and academician, who will be responsible for continued development of the department and will guide its research and education missions. Candidates (Ph.D. or M.D.) with strategic vision and a strong record of research in any area of the physiological sciences will be considered. Excellent interpersonal skills, scientific leadership, and commitment to mentoring junior faculty are essential. Credentials appropriate for the rank of Professor are required. Areas of ongoing funded research within the department include cancer biology and reproductive, gastrointestinal, and cardiovascular physiology. Additional information is available at **http://www.msm.edu/physiology/index.htm**. Opportunities for collaboration and program development within the institution are available through the Center for Reproductive Science, Cardiovascular Research Institute, Neuroscience Institute, Clinical Research Center, Cancer Biology Program, and other basic and clinical departments. The Department of Physiology contributes to the integrated curriculum of the medical education program and to the training of graduate students through the interdisciplinary Ph.D. program in Biomedical Sciences.

Interested applicants should submit a curriculum vitae and a letter of interest, either electronically (**cbartlett@msm.edu**) or by mail:

Dr. Myrtle Thierry-Palmer, Chair
Physiology Chair Search Committee
Room 349 Hugh Gloster Building
Morehouse School of Medicine
720 Westview Drive, SW
Atlanta, GA 30310

Correspondence will be kept confidential. Review of candidates will begin as applications are received and continue until the position is filled.

The Morehouse School of Medicine is an Affirmative Action/ Equal Opportunity Employer.

CHAIR
DEPARTMENT OF
MOLECULAR GENETICS AND BIOCHEMISTRY
UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE

The University of Pittsburgh School of Medicine is seeking a chair for the Department of Molecular Genetics and Biochemistry. The department comprises 32 primary faculty members with a focus on basic research in Molecular Biology, Microbiology, Virology, Biochemistry and Developmental Biology, although candidates working within any area of Molecular Genetics and Biochemistry are encouraged to apply. The successful candidate must demonstrate an outstanding record of scholarship commensurate with appointment at the rank of Full Professor with tenure, and as the William S. McEllroy Professor.

The University of Pittsburgh School of Medicine is enjoying unparalleled growth in its research, clinical, and academic missions. Of more than 3,000 institutions nationwide, the University of Pittsburgh is currently ranked 7th among educational and research institutions in NIH funding. As chair of Molecular Genetics and Biochemistry, the successful candidate will have an outstanding opportunity to add further to the growth of the basic biomedical sciences in the School of Medicine.

Please send curriculum vitae and bibliography to the MGB Chair Search Committee at: **biojobs@pitt.edu**.

The University of Pittsburgh is an Affirmative Action, Equal Opportunity Employer. Women and members of minority groups under-represented in academia are especially encouraged to apply.

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Tenure-Track Faculty Position in Immunobiology

The Center for Immunobiology in conjunction with the Division of Rheumatology at the Indiana University School of Medicine, is seeking **two outstanding investigators with expertise in the immunopathogenesis of rheumatic diseases**. Under the direction of David S. Wilkes, M.D., the Center for Immunobiology, within the School of Medicine, brings together basic, clinical and translation research focused on the immunological basis of disease. The Division of Rheumatology under the direction of Rafael Grau, M.D. is interested in strengthening its translational research goals through close interaction with basic science investigators.

Candidates for the current positions must have a doctoral degree and an outstanding publication record. This is a **tenure-track position for a Ph.D, M.D., or M.D./Ph.D. in the Department of Medicine with appropriate secondary appointments in basic science departments**; rank and salary will be commensurate with experience.

Send curriculum vitae, a 2 - 3 page statement of research interests and future plans, and the names and contact information of three professional references by e-mail to: **David S. Wilkes, M.D., Dr. Calvin H., English Professor of Medicine, Microbiology and Immunology, Director, Center for Immunobiology, Indiana University School of Medicine, Van Nuys Medical Sciences Building MS224, 635 Barnhill Dr., Indianapolis, IN 46202-5120, fax: 317-278-7030, email: dwilkes@iupui.edu, http://cimb.medicine.iu.edu/**

Indiana University School of Medicine is an Equal Employment Opportunity/ Affirmative Action Employer M/F/D.

香港城市大學
City University of Hong Kong

City University of Hong Kong is one of eight higher education institutions directly funded by the Government of the Hong Kong Special Administrative Region through the University Grants Committee (Hong Kong). It aims to become one of the leading universities in the Asia-Pacific region through excellence in professional education and applied research. In two studies, City University of Hong Kong ranks among the top 200 universities in the world, and among the top ten universities in the Greater China region. The mission of the University is to nurture and develop the talents of students and to create applicable knowledge in order to support social and economic advancement. The student population is approximately 26,000 enrolled in over 180 programmes at the associate degree, undergraduate and postgraduate levels. The medium of instruction is English.

The University invites applications and nominations for the following post. Candidates with applied research achievements will receive very positive consideration. Relevant experience in business and industry will be a definite asset.

Head of Department of Biology and Chemistry *[Ref. A/487/49]*

The Department of Biology and Chemistry comprises 27 faculty members and runs three undergraduate programmes (Applied Biology, Applied Chemistry, Environmental Science and Management), and one postgraduate programme (Environmental Science and Technology) for over 330 students. The Department places equal emphasis on teaching and applied research. Staff expertise lies in marine and coastal biology; pollution biology and chemistry; ecotoxicology; analytical and environmental chemistry. Other areas of focus such as green chemistry, environmental health and food safety, and nano-biovector are emerging fields which we built upon the interdisciplinary strength of biology and chemistry within the Department.

The Department has aound 70 PhD and 50 MPhil students pursuing their postgraduate studies in these areas. In addition, there are 90 research fellows/research assistants working with academic staff on a variety of funded research projects. Since 1990, members of the Department have attracted more than HK$354.4 million of competitive research grants and completed more than 350 consultancy studies for the Government and industries. Outstanding achievement in environmental research is reflected by the Centre for Marine Environmental Research and Innovative Technology (MERIT) supported by a HK$45 million Area of Excellence Grant from the Government.

Qualifications for Appointment
The Head of Department will provide strong academic leadership in the development of teaching and applied research within the Department, as well as providing effective managerial leadership. Candidates should possess strong academic and professional qualifications, substantial relevant experience in tertiary education, and an internationally recognized record of research and scholarship.

Salary and Conditions of Service
The successful candidate will be offered appointment to an academic rank commensurate with qualifications and experience. The appointment will either be on superannuable terms with provision for superannuation benefits, or on a fixed-term contract with contract-end gratuity. Concurrently, the appointee will be offered the headship appointment for an initial period of three years. The University offers competitive salaries and employee benefits, including annual leave, medical and dental schemes, housing benefits and, where applicable, passage allowance.

Information and Application
Further information on the post and the University is available at http://www.cityu.edu.hk or from the Human Resources Office, City University of Hong Kong, Tat Chee Avenue, Kowloon, Hong Kong [Fax : (852) 2788 1154 or (852) 2788 9334/ email: hrklau@cityu.edu.hk]. Please send the nomination or application in the form of an application letter, enclosing a current curriculum vitae, to the Human Resources Office by **20 March 2007**. Please quote the reference of the post in the application and on the envelope. The University reserves the right to consider late applications and nominations, and to fill or not to fill the position.

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Faculty Positions At MIT, McGovern Institute For Brain Research

The McGovern Institute for Brain Research at MIT is seeking two faculty members at the Assistant Professor, Associate Professor or Professor level. The McGovern Institute's general focus is in systems neuroscience with an emphasis on the neural basis of perception, cognition, and action. We are seeking two candidates with a research focus in any of these three areas, one using human subjects and the other using animal models. We would regard it as a plus if the candidate's work bridges levels using a variety of tools and/or the candidate were interested in translating basic research findings into new ideas for studying the pathophysiology or treatment of brain disorders.

The mission of the McGovern Institute is to understand the relationship of neuronal processes, circuits and computations to behavior, ultimately providing benefits to human health and welfare. Research in the McGovern Institute is expected to help people with brain disorders ranging from sensory system impairments to movement disorders and emotional and cognitive disorders. McGovern Institute scientists have many opportunities for collaboration in a diverse and cutting-edge environment. In the fall of 2005, the Institute moved to occupy a new building, which includes a brain imaging center for human subjects and animals.

Applicants should submit a curriculum vitae, a summary of current and proposed research programs, and should arrange for three letters of recommendation to be sent electronically (preferably PDF) to the McGovern Institute Search Committee, at the following email address: McGovernInstituteSearch@mit.edu. Please indicate which of the two positions you are applying for in your cover letter. Consideration of applications will begin on March 1, 2007. For more information on the McGovern Institute please visit our website at http://web.mit.edu/mcgovern

MIT is an Affirmative Action/Equal Opportunity Employer.
Qualified women and minority candidates are especially encouraged to apply.

http://web.mit.edu

HEMATOLOGY-ONCOLOGY PHYSICIANS

St. Jude Children's Research Hospital is seeking hematology-oncology physicians to provide patient care and participate in ongoing clinical investigations for children with hematological disorders. Candidates should have MD (or equivalent) degrees, experience in patient diagnosis and management, and a background in clinical trials relating to hematology and/or oncology. Opportunities for laboratory-based research may also be available. Associations with the University of Tennessee Health Science Center College of Medicine and the Department of Pediatrics at Le Bonheur Children's Medical Center provide opportunities for teaching students, residents and fellows. The facilities and salaries are competitive.

Send a CV and letter of inquiry (referencing #070NC) to:

Cynthia Brock
Human Resources, Mail Stop 507
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis TN 38105

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Rated No. 1 in **The Scientist's** *"Best Places to Work 2006" listing.*

Positions @ NIH

THE NATIONAL INSTITUTES OF HEALTH

NIEHS
National Institute of Environmental Health Sciences
National Institutes of Health

Functions of Sir2 and Nuclear Receptors

Research Triangle Park, North Carolina

Postdoctoral positions are available immediately in the Laboratory of Signal Transduction at the National Institute of Environmental Health Sciences (NIEHS), a major research institute of the NIH located in Research Triangle Park, North Carolina. NIEHS offers an outstanding research environment and has been constantly rated by The Scientist as one of the best places for post-docs to work.

Our research is focused on the roles of NAD+-dependent protein deacetylase Sir2 and corresponding post-translational modification of nuclear receptors in aging and age-associated diseases. We have shown that SIRT1, the mammalian orthology of Sir2, physically interacts and deacetylates Liver X Receptors (LXRs), thus regulates their transcriptional activity and cholesterol homeostasis. Current research areas include nuclear receptor signaling pathways regulated by SIRT1 and their roles in metabolism, aging, and metabolic diseases such as atherosclerosis and obesity.

We seek highly self-motivated individuals who have a strong background in signaling and transcriptional/translational regulation, and are interested in aging research. Experience with mouse models is a plus. To apply, please send a cover letter, CV and list of three references to Dr. Xiaoling Li at email: lix3@niehs.nih.gov.

U.S. Department of Health and Human Services
National Institutes of Health

DHHS and NIH are Equal Opportunity Employers

NIEHS
National Institute of Environmental Health Sciences
National Institutes of Health

Staff Scientist in Protein Biochemistry

Research Triangle Park, North Carolina

The Laboratory of Signal Transduction at the National Institute of Environmental Health Sciences is recruiting a staff scientist in support of the Transmembrane Signaling Group headed by Dr. Lutz Birnbaumer. The incumbent will oversee group efforts in studying molecular mechanisms involved in the activation of G proteins by guanine nucleotide exchange factors, including the interaction of genetically engineered rhodpsins with transducin extracted and purified from mammalian retinas. The selectee will be expected to personally execute experiments, oversee up to three technical support personnel and train and supervise group graduate students and postdoctoral fellows in the conduct of this area of research. The successful candidate is expected to work with minimal guidance, carry the research to publishable stages and work on these and other projects as defined by the group leader.

Minimum qualifications include a doctoral degree, successful completion of postdoctoral training, record of publications and strong background in protein purification techniques and analysis of enzymatic and physicochemical properties of mammalian and recombinant proteins.

For additional information, contact Dr. Lutz Birnbaumer at birnbau1@niehs.nih.gov. For additional information concerning the research projects and publications, visit the following website: **http://dir.niehs.nih.gov/dirlst/groups/birnbaumer.htm**. Applications from women and minorities are particularly encouraged. To apply, submit a curriculum vitae, bibliography, brief statement of research interests and arrange for three letters of recommendation to be sent by **March 16, 2007**, to the address indicated below. Applications received after that date will be considered as needed:

Mr. Will Williams (DIR-07-02)
National Institutes of Health • National Institute of Environmental Health Sciences
P.O. Box 12233, Maildrop A2-06 • 111 Alexander Drive, Room A202
Research Triangle Park, NC 27709
e-mail: **dir-appls@niehs.nih.gov**

DHHS and NIH are Equal Opportunity Employers

U.S. Department of Health and Human Services
National Institutes of Health

Tenure/Tenure-Track Investigator in HIV Research
Laboratory of Molecular Microbiology

NIAID's Laboratory of Molecular Microbiology (LMM) is seeking a viral immunologist for a tenure-track (assistant professor) position to develop an independent research program focusing on the immune responses to primate lentiviruses. Candidates should have an M.D, Ph.D. or D.V.M degree. The ideal candidate will have extensive research accomplishments in viral immunology in the context of primate lentivirus pathogenesis and vaccine development.

This position provides access to modern research facilities and technologies including flow cytometry, DNA sequencing, oligonucleotide and peptide synthesis, confocal/light microscopy, microarrays, proteomics, and mass spectrometry. A competitive federal salary and benefits package will be provided, along with an operating budget for equipment, supplies, and staff.

Questions about this position can be sent to **Dr. Malcolm Martin at malm@nih.gov**. To apply, submit a curriculum vitae, bibliography and 2-3-page description of a proposed research program, preferably via e-mail to **Ms. Felicia Braunstein at braunsteinf@niaid.nih.gov**. In addition, three letters of recommendation must be sent to **Ms. Felicia Braunstein, NIAID, NIH; Bldg. 10, Rm. 4A31, MSC-1356; Bethesda, MD 20892-1356**. Applications must be received by **February 28, 2007**. Please note search **#007** in all correspondence. Applicants will be notified by e-mail or phone phone when their applications are received and complete.

Please see our web site at **http://www.niaid.nih.gov/dir/labs/lmm.htm** for information about current LMM principal investigators and their research interests.

The NIH Director's Wednesday Afternoon Lecture Series

Biomedical scientists around the world are invited to join us online to hear leading investigators present their latest results to the NIH Intramural Research community. Lectures may be viewed live at 3:00 p.m., EST (20:00 GMT) on Wednesdays, from September through June. Live webcasts can be viewed under "Today's Events" at: <http://videocast.nih.gov/>

The current schedule of lectures is available at: <http://www1.od.nih.gov/wals/schedule.htm>

Upcoming Lectures:

•January 24: Robert G. Griffin, MIT, Cambridge, MA: Solid State NMR of Membrane and Amyloid Proteins

•January 31: Clara Franzini-Armstrong, University of Pennsylvania: Protein Interactions in Calcium Release Units of Skeletal and Cardiac Muscles

•February 21: Marc G. Caron, Duke University Medical Center: Novel GPCR Signaling Paradigms in Animal Models

•February 28: L. Mahadevan, Harvard University: Mathematics, Mechanics and Motility

WWW.NIH.GOV

Tenure-Track and Tenured Investigator Positions in Systems Immunology and Infectious Disease Modeling

The National Institute of Allergy and Infectious Diseases (NIAID), Division of Intramural Research (DIR) is seeking several outstanding individuals for its new Program in Systems Immunology and Infectious Disease Modeling (PSIIM).

Modern technology allows the analysis of immune responses and host-pathogen interactions at multiple levels—from intracellular signaling networks, to individual cell behavior, to the functioning of a tissue, organ, or even whole organism. The challenge is not only to collect large amounts of data, but also to organize it in a manner that enhances our understanding of how the immune system operates or how pathogens affect their hosts. To do this, we need to develop detailed quantitative models that can be used to predict the behavior of a complex biological system. These models can help to explain the mechanisms underlying physiological and pathological responses to infection or vaccination, which can then be exploited to design better therapies or vaccines.

Achieving this goal requires an interdisciplinary effort and to this end the PSIIM will be organized as an integrated team of scientists and support staff with expertise in computational biology, bioinformatics, proteomics, cell biology, immunology, and infectious diseases, rather than as a group of independent laboratories. These teams will have access to the latest technology for gene-expression profiling, high-content screening of RNAi libraries for the discovery of pathway components, imaging tools, cores for the genetic manipulation of animals and for proteomic analysis, and a substantial computer infrastructure. BSL-3 facilities for working with high priority pathogens will also be available.

Although the PSIIM has been established within NIAID and has an immune system/infectious disease focus, we expect it to foster the growth of systems biology efforts at other NIH Institutes, primarily through the development of new software tools for complex systems modeling and methods for high-throughput screening. Thus, PSIIM team members are expected to interact extensively with other NIH scientists and with extramural groups in the U.S. and abroad who share our interest in a systems approach to biology.

The PSIIM is now recruiting for tenure-track or tenure level team leader appointments in three key areas:

Computational Biology: The incumbent will lead a group focused on the development and improvement of software tools for multiscale modeling and simulation that can be used by the PSIIM as well as by biologists interested in subjects other than immunity or infectious diseases. The ideal candidate will have a strong background in mathematics, physics, and computer programming, and a clear desire and ability to interact with and support the efforts of biologists. A demonstrated ability to generate computer software tools for biological modeling will be a strong plus.

Molecular/Cell Biology: The incumbent will lead a group involved in the design, implementation, and interpretation of screening efforts to identify and determine the interactions among the components in signaling networks that could then be modeled using the software generated by the computational biology team or obtained from other sources. Discovery tools such as gene arrays, high-content image-based screens using RNAi methods, various protein-protein hybrid screening methodologies, and optical imaging are expected to be key elements in the efforts of this group. A strong background in basic cell biology and molecular biology with experience in analysis of protein-protein interactions, signaling, and/or gene regulation is required. Expertise in large-scale screening is highly desirable.

Infectious Diseases: The incumbent will be responsible for developing novel approaches to systems-wide analysis of the interaction of infectious agents and their hosts. These may include the use of gene-expression signatures, the production of gene-modified animals, the development of methods for in vivo testing of the predictions of models, and the use of sophisticated imaging and other tools for probing the interaction of pathogens and host cells in vitro. A strong background in viral and/or bacterial infectious diseases and cell and molecular biology are necessary; training in the immunology of infectious diseases and substantial bioinformatics experience are highly desirable.

These positions and the research activities they conduct are fully funded by the intramural research program of NIH. Each team leader is expected to build a working group consisting of postdoctoral fellows, staff scientists, technicians, and students. The team leaders will work with the program director to help set the goals for the PSIIM and to determine how best to reach these goals as an integrated group. To ensure appropriate career trajectories for those joining the PSIIM team, the NIH has modified its tenure decision policies to encourage and account for contributions made in such a team science setting. Applicants should be seeking a difficult challenge in which creativity, technical expertise, and a strong desire to achieve in a team environment are critical for success.

Interested candidates may contact **Dr. Ronald Germain, Program Director, PSIIM, DIR, NIAID at 301-496-1904 or rgermain@niaid.nih.gov** for additional information about these positions.

To apply, submit your curriculum vita, bibliography, and detailed statement of how you can contribute to the success of the PSIIM program to **Felicia Braunstein at braunsteinf@niaid.nih.gov**. In addition, three letters of reference must be sent directly from the referee to **Dr. Robert Hohman, Chair, NIAID Search Committee, c/o Ms. Felicia Braunstein, DIR Committee Management Team Lead, 10 Center Drive, MSC 1356, Building 10, Room 4A31, Bethesda, Maryland 20892-1356**. Completed applications **MUST** be received by **February 16, 2007** for computational biology, and **March 16, 2007** for Molecular/Cell Biology as well as for infectious diseases. Please refer to ad **#012 for computational biology, #013 for molecular/cell biology, and #014 for infectious diseases** on all correspondence. Further information on these positions and guidance on submitting your application are available at **http://healthresearch.niaid.nih.gov**. For more information about the NIAID systems biology program, please visit **http://www.nih.gov/catalyst/2006/06.09.01/page1.html**

FACULTY POSITIONS

MASSACHUSETTS GENERAL HOSPITAL

is recruiting faculty in Sarcoma Biology for a newly created, multi-disciplinary lab within the Department of Orthopaedic Surgery (faculty member of Harvard Medical School). Post Doctorate or Instructor Level position is available specifically focused on the basic understanding and manipulation of sarcoma cells to provide detailed analyses of sarcoma by micro array analyses in the hope of providing new insights to drug development. Interest – mechanism of drug resistance by sarcomas. The incumbent would interact with industry in the development of new chemotherapeutic drugs and with scientists in Radiation Oncology, Pathology, and Surgical Oncology. The Orthopaedic Department research program emphasizes the biology of skeletal tissues with a focus on osteoarthritis, bone defects, healing, and bone tumors. This recruitment prioritizes basic cell biologic investigation as a base for translation into practical applications in human disease. The centers participate fully in the Dana Farber Harvard Cancer Care initiatives or mission and graduate programs; the laboratory is on the MGH main campus. We are seeking Ph.D. scientist with a proven track record of innovative, interactive research.

Candidates should send a letter of interest including research plans, C.V. and 3 letters of support to: **Dr. Francis H. Hornicek, M.D., Ph.D., Department of Orthopaedic Surgery, Massachusetts General Hospital, 55 Fruit Street, YAW-3700, Boston, MA 02114; Email: Lmcneil1@partners.org.**

CHIEF SCIENTIST

NATIONAL ECOLOGICAL OBSERVATORY NETWORK

The National Ecological Observatory Network office (NEON: www.neoninc.org), managed by the nonprofit NEON Corporation (NEON Inc.), has an immediate opening for a full-time Chief Scientist to oversee the development of NEON's scientific capabilities. This position will be based in Boulder, Colorado with the potential to start as soon as 15 February 2007.

NEON is a Major Research Equipment and Facilities Construction project being developed for the National Science Foundation. The goal of NEON, Inc. is to deliver a continental-scale research instrument consisting of geographically distributed and networked infrastructure, including lab and field instrumentation, site-based experimental infrastructure, biodiversity archive facilities, and computational, analytical, and modeling capabilities.

JOB DESCRIPTION: Reporting to the Chief Executive Officer, the Chief Scientist shall lead NEON's science functions and provide strategic guidance for the management, design, and development of the scientific infrastructure. This effort includes but is not limited to: (A) Ensuring that the science undertaken by NEON is founded on the best and most current scientific understanding, (B) Ensuring that NEON scientific capabilities are translated into a robust networked infrastructure, which requires working with the NEON Facilities Manager and each of the twenty lead Domain scientists to deploy the scientific infrastructure across the Nation, and (C) Ensuring that NEON scientific capabilities are supported by NEON's cyberinfrastructure, which requires working with the scientific community to define data collection protocols, QA/QC protocols (for both instruments and field campaigns), and data product algorithms. The Chief Scientist shall also work closely with NEON's cyberinfrastructure partners to translate these data requirements into system design specifications.

SKILLS, EXPERIENCE, AND QUALIFICATIONS: The successful candidate should possess a PhD degree in a related field. The candidate should have 10 years professional experience in a leadership role with substantial supervisory responsibilities. Experience in research on large scale ecological processes, a demonstrated ability to lead large collaborative scientific efforts, and prior experience working with cyberinfrastructure specialists to develop scientific data systems is a plus. Strong communication and interpersonal presentation skills are key, owing to the extensive interaction across a broad range of individuals with diverse scientific backgrounds.

TO APPLY: Applications will be reviewed starting mid **February 2007**. This position will remain open until filled. Travel will be required and salary is commensurate with experience. This is a full-time, salaried position subject to the continuing availability of NSF funding. Benefits include health care, paid vacation, and retirement plan. Send cover letter, resume, salary history, and salary requirements to: **NEON Administrative Director, attn. NEON Chief Scientist Search, AIBS, 1444 Eye St. NW, Suite 200, Washington, DC 20005; FAX; 202-628-1509; bwee@aibs.org**.

FACULTY POSITIONS

University of Massachusetts Medical School
UMASS

FACULTY POSITIONS, DIABETES CENTER

The Diabetes Center at the University of Massachusetts Medical School invites applications for **JUNIOR TENURE-TRACK** and **SENIOR TENURED** faculty positions. This newly established multi-disciplinary Center seeks basic scientists and physician scientists with research experience relevant to the fields of either type 1 or type 2 diabetes and metabolic disease. The Diabetes Center seeks to build upon its substantial diabetes clinical and research program to enhance its leadership in developing innovative clinical care and discovery of new therapeutic modalities. The Diabetes Center will be housed in a new building designed to integrate clinical service and research activities performed by teams of outstanding faculty. There is particular interest in strengthening the areas of beta cell biology, autoimmunity and clinical studies on mechanisms of metabolic abnormalities in humans. Faculty appointments will be made within the Department of Medicine or other Clinical and Basic Science Departments as appropriate.

The faculty positions will be highly competitive with regard to start up funds and guaranteed salary for up to 5 years. Faculty recruits will have full access to the outstanding scientific environment at the Medical School, including extensive Core facilities that support work in genetically modified animals, genomics/proteomics, bioinformatics, imaging, RNAi and small molecule screening. Emphasis in recruiting will be placed on translational research and particularly attractive packages will be available to clinical researchers committed to this focus.

Applicants should send curriculum vitae, statement of research interests, and names and addresses of three references to: **Dr. Aldo Rossini, Director, or Dr. Michael P. Czech, Search Committee Chair, Diabetes Center, University of Massachusetts Medical School, 373 Plantation Street, Suite 100, Worcester, MA 01605.**

The University of Massachusetts Medical School is an Equal Opportunity/Affirmative Action Employer.

PURDUE UNIVERSITY

Head, Department of Physics

Applications are invited for the position of Head of the Department of Physics at Purdue University from dynamic individuals with creative vision and an outstanding record of research accomplishments. The department, one of the seven departments of the College of Science, has over 50 faculty members, with active research programs in astrophysics, accelerator mass spectrometry, biophysics, condensed matter physics, elementary particle physics, geophysics, nanophysics, nuclear physics, sensor technology, and physics education. Department faculty are involved in University-wide multidisciplinary research through Discovery Park, a group of interdisciplinary research centers **http://discoverypark.purdue.edu/wps/portal** and the College of Science **http://www.science.purdue.edu**. The department has implemented a strategic plan for future growth supported by the higher administration. Further information about the department can be found at **http://www.physics.purdue.edu**.

The successful candidate will have an outstanding record of scholarly achievement commensurate with the rank of full professor at Purdue, exceptional and proven leadership qualities and administrative abilities, a vision of the role of the physics department in the university, state and nation, and the skills to communicate it. In addition to a strong research program, we seek a commitment to teaching excellence, and a commitment to diversity. Qualified persons should submit a letter of application, a research statement, a teaching statement, a vision statement, and complete curriculum vitae with addresses and email addresses of four references. Review of applications will begin March 15, 2007 and will continue until the position is filled. Send applications, nominations and inquiries to: **h-search@physics.purdue.edu**. Hard copy applications may be sent to: **Ian Shipsey, Head Search Chair, Department of Physics, 525 Northwestern Avenue, Purdue University, West Lafayette, IN 47907-2036.**

Purdue University is an Equal Opportunity/Equal Access/Affirmative Action employer committed to building a diverse faculty of excellence.

I want to be part of an innovative workplace.

You can at AstraZeneca. Discover your potential with a global pharmaceutical industry leader who values your contributions, seeks innovation, and rewards success.

We are establishing a discovery research center with cutting edge science and technology in **Shanghai, China**. Innovation Center China will initially concentrate on cancer research, with a focus on translational science by developing knowledge about Chinese patients, biomarkers and genetics.This is one of the largest investments made by a multinational pharmaceutical company in China and AstraZeneca is excited to contribute to the increasing number of scientific innovations in this country.

We have opportunities available for highly motivated scientists and lab technicians who want to take an innovative approach to their career. Candidates with industry experience, especially in the area of cancer research, are encouraged to apply. We are recruiting individuals with experience in the following areas:

- **Tumor biology**
- **Signal transduction**
- **Molecular and cell biology**
- **Cell based assay**
- **Tissue banking and tracking**
- **Pathology**
- **Tumor genetics**
- **DNA sequencing**
- **FISH and aCGH**
- **Gene expression and microarray**
- **IHC**
- **Informatics**
- **Statistical data analysis**

Please visit **http://en.astrazeneca.com.cn** to view our current openings and to apply. We are an equal opportunity employer.

Visit our booth at the 2007 AACR Conference in Los Angeles this April.

AstraZeneca

Sunnybrook
RESEARCH INSTITUTE

Scientist Positions

The Sunnybrook Research Institute (SRI) at Sunnybrook Health Sciences Centre invites applications for both senior and junior positions. Applicants with competitive research programs in the molecular, cellular, or genetic basis of disease, systems biology, developmental biology, cellular signaling or inflammation, must hold a Ph.D. and/or M.D. degree, have a strong record of research accomplishments, and be eligible for academic appointment at the University of Toronto.

Fully affiliated with the University of Toronto, the SRI is comprised of four Research Disciplines: Clinical Epidemiology, Clinical Integrative Biology, Imaging, and Molecular & Cellular Biology [www.sunnybrook.ca/research]. With annual extramural funding of more than $85M, research activity by the 180 faculty at SRI is housed within 250,000 sq.ft. of state-of-the-art research space, with 130,000 sq.ft. of new space to be completed by 2009. SRI offers full salary, benefits and pension plan, and provides excellent core infrastructure support including: facilities for imaging, histology, hybridoma production, flow-cytometry and scanning microscopy, proteomics, genomics, transgenesis and gene targeting. A major centre for graduate education through cognate University of Toronto Departments, there are over 200 graduate students and postdoctoral fellows currently training at SRI.

Researchers within the Discipline of Molecular and Cellular Biology are internationally competitive in areas including the analysis of the genetic and biochemical basis of: immune system development, oncogenesis, cell signaling, cell cycle regulation, disease susceptibility, angiogenesis and vascular modeling, and imaging guided early detection of cancer.

Curriculum vitae and details of research activities can be submitted electronically or by mail to: **Daniel Dumont, Ph.D., Director, Molecular and Cellular Biology, Sunnybrook Research Institute, 2075 Bayview Avenue, Room S2-18, Toronto, Ontario, M4N 3M5; dan.dumont@sri.utoronto.ca.**

Sunnybrook Health Sciences Centre and the University of Toronto are committed to employment equity and welcome applications from all qualified women and men, including visible minorities, aboriginal people, persons with disabilities, and persons of a diversity of sexual orientation.

GRANTS

European Commission 6th Framework Program
EURASNET
Network of Excellence (2006-2010)

EURASNET

SIXTH FRAMEWORK PROGRAMME

Open Call for the Young Investigators Program

30 European Scientists have established EURASNET, the European alternative splicing network. EURASNET is a Network of Excellence consortium within the 6th Framework Program (FP6), and integrates European research on alternative splicing. To promote new groups working on alternative splicing, EURASNET will include five Young Investigator Teams. They will have full access to EURASNET activities and a three-year research grant totaling 120,000 €. Applicants should be within their first three years of independent research at the time of their application, hold a position in an institute eligible for FP6 funding, and be willing to contribute towards the Joint Program of Activities.

Deadline for applications: **March 7, 2007**

For information about EURASNET and how to apply, please direct your browser to:

www.eurasnet.info

PROJECT DIRECTOR
Ref: ESSPD

The ESS-Bilbao Consortium representing the Spanish candidature to host the European Spallation Source in Bilbao, Basque Country, Spain, is searching for a PROJECT DIRECTOR. A professional in the field of Neutron Physics and Engineering and/or Neutron Scattering Techniques with an established record of significant scientific accomplishment and leadership will fill the position.

The ESS-Bilbao Consortium is a newly established organization created with the mission to promote and consolidate the Spanish candidature to host the European Spallation Source in a scientific, technical, economic and administrative way.

The Project Director will be responsible together with the Executive Committee President for achieving the consortium goals. He/she will be involved in the promotion and coordination of the candidature and will oversee organization, as well as the implementation of pending technical issues alongside with establishing international collaborations.

We are looking for a highly qualified person with proven experience in Neutron Physics and Engineering and/or Neutron Scattering Techniques research. Experience on international managing teams and understanding of development functions and procurement funds are essential, ideally with an international network of contacts.

Excellent command of English is indispensable, both oral and written, a second European language is an asset; good presentation and communications skills. Knowledge of Spanish is not a requirement.

The ESS-Bilbao Consortium offers a challenging position and salary depending upon proven experience. Applicants should forward their CV and contact information for two referees by **February 28, 2007** by post mail or e-mail to:

Ms. Cristina Oyón
REF. ESSPD
Parque Tecnológico de Bizkaia
Laida Bidea Ed 214
E- 48170 Zamudio
SPAIN

cristinaoyon@essbilbao.com
www.essbilbao.com/html/Employment

ESS- Bilbao Consortium is an Equal Opportunity Employer.

FACULTY POSITIONS

DIRECTOR
Proteomics Core Laboratory

Candidates are sought for the position of Proteomics Core Laboratory (PCL) Director in the College of Medicine at the University of Toledo Health Sciences Campus (formerly Medical University of Ohio). Applicants must have an M.S. or Ph.D. in a relevant field, and direct experience with electrophoretic methods of protein separation, liquid chromatography, and mass spectrometric analysis of proteins including sequence determination. Experience with antigen-antibody arrays in proteomic quantification will be considered an advantage. The successful applicant will assist University researchers in planning and interpreting proteomics-based projects, and oversee daily operations of the PCL including supervision of a technician. Candidates with an independent research program could be considered for faculty rank in an appropriate academic department. The PCL is located in brand new laboratory space, and includes a MALDI-ToF and an ion-trap tandem mass spectrometer, **website: http://hsc.utoledo.edu/depts/bioinfo/cores/protintro.html.** Send curriculum vitae that specifically includes a description of relevant experience, cover letter, and contact information (including telephone numbers and e-mail addresses) for three referees. Materials should be sent to: **Proteomics Core Laboratory Director Search, c/o Ms. JoAnne Gray, Program in Bioinformatics and Proteomics/Genomics, Room HEB-121, University of Toledo Health Science Campus, Toledo, OH 43614-5804;** or e-mailed to **e-mail: jgray@meduohio.edu.**

Inquiries may be addressed to the **Program Director, e-mail: robert.blumenthal@utoledo.edu.**

POSITIONS OPEN

HARVARD MEDICAL SCHOOL
Children's Hospital Boston

POSTDOCTORAL or **INSTRUCTOR** level positions to study the impact of inflammatory pathways on the development of pulmonary hypertension and cardiopulmonary pathologies using animal models of lung disease and stem cell-based interventions. Applicants should have a Ph.D. or equivalent degree and fluency in English is essential. Strong background in molecular biology, stem cells, oxidant stress, inflammation, or histopathology is highly desirable. Send curriculum vitae, a brief summary of research interests plus three references to:

Stella Kourembanas, M.D.
Clement A. Smith Chair of Pediatrics, Chief
Division of Newborn Medicine
Children's Hospital Boston
300 Longwood Avenue - Enders 960
Boston, MA 02115

Or **e-mail: stephanie.giannetto@childrens.harvard.edu.**

CHILDREN'S HOSPITAL
Harvard Medical School
Division of Respiratory Diseases

The Division of Respiratory Diseases is searching for a **BASIC SCIENTIST** (Ph.D. M.D. or M.D./Ph.D.) to establish a laboratory investigating linkages between adipocyte biology and inflammation. The successful candidate will have an established interest in this or other emerging areas of inflammation biology. Rank will be commensurate with experience, and a generous recruitment package is available. The Children's Hospital is in the heart of the Longwood Medical Area and Harvard Medical School, and is a resource-rich collaborative environment. Women and minorities are encouraged to apply to: **Prof. Craig Gerard, Chair, Search Committee, 300 Longwood Avenue, Boston, MA 02115 (e-mail: craig.gerard@childrens.harvard.edu).** Letters of reference from at least three senior investigators should accompany the application. *Children's Hospital is an Equal Opportunity Employer.*

FACULTY POSITIONS

MOLECULAR GENETICIST/BIOLOGIST
ASSISTANT PROFESSOR
Tenure Track, Academic Year 100 Percent

The Department of Biology, University of Wisconsin-La Crosse, invites applications for an academic year, tenure-track position at the level of Assistant Professor. The successful candidate will teach genetics or cell biology, and develop a course in her/his area of expertise (population genetics, molecular evolution, genomics, or signal transduction desirable). Applicants must have a strong commitment to undergraduate education. A Ph.D. in a biological science is required. Some previous teaching experience is desirable. Successful candidates will be expected to develop an externally funded research program and direct undergraduate and graduate (M.S.) research. Academic year salary competitive and commensurate with experience. Start August 27, 2007. Applicants should submit letter of application, curriculum vitae, statements of teaching philosophy and research interests, graduate and undergraduate transcripts, and three letters of recommendation to: **Dr. Mark Sandheinrich, Department of Biology, University of Wisconsin-La Crosse, La Crosse, WI 54601.** Applications must be received by March 30, 2007, and electronic applications will not be accepted. *As an Affirmative Action Equal Opportunity Employer, the University of Wisconsin-La Crosse is engaged in an effort to be a leader in Wisconsin's movement toward increased diversity and indusiveness. Women, persons of color, and individuals with a disability are encouraged to apply. If you have a special need/accommodation to aid your participation in our hiring process, please contact* ***Mark Sandheinrich (e-mail: sandhein.mark@uwlax.edu)*** *to make appropriate arrangements.*

ASSISTANT PROFESSOR
Division of Research
Department of Pathology
Louisiana State University School Health Sciences Center, Shreveport

The Division of Research within the Department of Pathology at Louisiana State University Health Sciences Center, Shreveport, is seeking applicants for a tenure-track appointment at the Assistant Professor level. This position is open to individuals possessing Ph.D., M.D., or M.D. Ph.D. degrees. The ideal candidate should have expertise in one or more of the following areas: molecular/cell biology of extracellular matrix molecules, angiogenesis, cell adhesion and signaling, and/or vascular wall pathology. Applicants with expertise in the above areas especially in the context of diabetic complications are particularly encouraged to apply. The selected candidate will have limited personal teaching/clinical responsibilities, primarily defined by his/her interests and training. Applicants should submit curriculum vitae, list of at least three references, and a brief description of research interests and direction by March 30, 2007, to: **Kevin McCarthy, Ph.D., Professor, Department of Pathology, Louisiana State University Medical Center in Shreveport, P.O. Box 33932, Shreveport, LA 71130.** *Louisiana State University Medical Center is an Affirmative Action Employer.*

POSITIONS OPEN

POSTDOCTORAL POSITION

BioT Incorporated seeks five **MOLECULAR BIOLOGISTS** for the R&D Department. The position requires experience in (1) Isolation and purification of RNA from tissues, cells, bacteria, and virus, (2) Messenger RNA quantitation using PCR, (3) Isolation of complementary DNA clones from RNA using real time polymerase chain reaction, (4) DNA sequencing, restriction enzyme digestion subcloning, plasmid construction and transfection. Full-time positions and salary $60,000 per year. *These positions require citizens of the Turkish Republic.* Interested applicants should send curriculum vitae to: **Associate Professor Dr. Şükran Sahin, R&D Coordinator, BioT Incorporated, Istanbul, Türkiye. Telephone: 90-216-449-25-15, e-mail: sukran@biotas.eu.**

POSITIONS OPEN

INSTITUTE OF BIOCHEMISTRY AND CELL BIOLOGY
Postdoctoral Fellowship
Wang Yinglai Postdoctoral Scholarship
Center for Cell Signaling

Positions for Institute of Biochemistry and Cell-Biology (IBCB) **POSTDOCTORAL FELLOWS** and Wang Yinglai **POSTDOCTORAL SCHOLARS** are available immediately at the Center for Cell Signaling (CCS), IBCB, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS). The Center provides a platform for the collaboration between investigators at IBCB and their overseas colleagues, working on the following research topics: **Jiarui Wu** (IBCB) and **Wei Du** (University of Chicago): Cell proliferation during normal development and tumorigenesis. **Xiaolong Liu** (IBCB) and **Hua Gu** (Columbia University): Signaling in hematopoietic stem cells and hematopoiesis. **Gang Pei** (IBCB) and **Jun-Lin Guan** (University of Michigan): Integrin signaling in breast cancer and embryonic stem cells. **Naihe Jing** (IBCB) and **Anning Lin** (University of Chicago): Signaling in neural stem cells, neural induction and cell death. **Chen Wang** (IBCB) and **Zhenggang Liu** (National Cancer Institute): Signaling in cell death, inflammation and tumorigenesis. **Lin Li** (IBCB) and **Dianqing (Dan) Wu** (Yale UniversityUniversity): Wnt signaling in stem cell biology. **Xueliang Zhu** (IBCB) and **Yixian Zheng** (Carnegie Institute of Washington): Cell polarity formation and mitosis.

Successful candidates will be recent Ph.D. graduates with a strong background in the relevant research fields. The Fellows or Scholars will enjoy a strong research environment and have the possibility to work abroad for a short period of time during the Fellow or Scholar tenure and to continue their study after successful completion of the fellowship or scholarship. The salary compensation will be highly competitive. In your application, please indicate the research area you are interested in. For more information, please see **website: http://www.sibcb.ac.cn/boshihouzp.asp.** Please e-mail your curriculum vitae and three reference letters to: **Mr. Banghe Mao, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. E-mail: bhmao@sibs.ac.cn.**

EXECUTIVE VICE PRESIDENT

National Disease Research Interchange (NDRI), a not-for-profit company providing scientists with human biomaterials for research, invites applications for Executive Vice President. The Executive Vice President will possess strong financial and organizational competencies with a minimum of ten years of experience working in a scientific environment requiring business management skills. Requires demonstrated success in negotiating sponsored research agreements, supervising technology joint ventures, and evaluating new science and technology.

Qualified candidates with an advanced degree in medicine or a Ph.D. in the biological sciences or medicine in molecular biology, immunology, genetics, pathology, or a related field are expected to have submitted successful grant applications to NIH and be familiar with NIH reporting requirements and leadership. Superior communication skills required. Computer expertise to include advanced spreadsheet, database, and reporting skills. Must have excellent analytic, writing, and presentation skills. An energetic team player committed to organizational growth and identification of new opportunities is required. Competitive salary and excellent benefits. E-mail curriculum vitae to **e-mail: smcgovern@ndriresource.org,** or fax to **S. McGovern** at **fax: 215-557-7154,** or mail to:

Attn: S. McGovern
1628 John F. Kennedy Boulevard
8th Floor, 8 Penn Center
Philadelphia, PA 19103

2 Great Career Events

Science/UCSF Biotech Industry Career Fair

(in partnership with AAAS Annual Meeting)

Science Careers and UCSF are co-hosting a career fair. Come meet recruiters face to face and explore career opportunities for all levels of scientists.

For information on exhibiting, contact Darrell Bryant at (202) 326-6533.

Thursday, 15 February 2007
1:00 pm – 4:30 pm
UCSF Mission Bay Campus
Robertson Auditorium
San Francisco, CA

More information on these events at
www.sciencecareers.org/ucsf

Making the Most of Your Career Fair

Attending the career fair? Learn how to market yourself at our free seminar.

Tuesday, 13 February 2007
6 pm —reception to follow
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Genentech Auditorium
San Francisco, CA

Making the Most of Your Career Fair is sponsored by Genentech

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Industry Recruiter

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FACULTY POSITIONS

DEVELOPMENTAL BIOLOGIST

The Biology Department of Albion College announces a search for an anticipated full-time, tenure-track Developmental Biologist at the rank of **ASSISTANT PROFESSOR,** to begin in August 2007. A Ph.D. is required. College teaching experience and a demonstrated record of scholarship are preferred. The successful candidate will be expected to teach a majors' course in developmental biology and develop a course in his or her area of expertise. The candidate also will share responsibilities in an introductory cell and molecular biology course. A research agenda that incorporates undergraduate students is expected. Facilities include a new, well-equipped, interdisciplinary science complex, state-of-the-art molecular biology equipment, a wide array of teaching and research-grade microscopes, and controlled-environment chambers. Albion College is a selective, liberal arts college of 1,900 students located in south-central Michigan, within an hour's drive of three major universities. See **website: http://www.albion.edu/biology/** for further information and a more comprehensive listing of instrumentation and resources. Send letter of application, statements on teaching and research interests, curriculum vitae, graduate and undergraduate transcripts, recent reprints, and three letters of reference (electronic copies not acceptable) to: **Dr. E. Dale Kennedy, Biology Department, Albion College, Albion, MI 49224-1831.** The deadline for completed applications is March 15, 2007. *Albion College is an Equal Opportunity Employer committed to diversity as a core institutional value.*

POSITIONS OPEN

PHYSICIST
National Institute of Standards and Technology

The Atomic Spectroscopy Group of the Atomic Physics Division of the National Institute of Standards and Technology (NIST)/U.S. Department of Commerce is seeking a Physicist with experience in atomic spectroscopy and database development for a permanent staff position at NIST in Gaithersburg, Maryland. The person selected will be expected to take a leading role in the NIST program of analysis and compilation of spectral lines, energy levels, and transition probabilities for atoms and atomic ions. He or she will also have responsibility for advancing state-of-the-art programming to further develop the NIST online databases for atomic spectral data. Applicants should have a Ph.D. and/or experience in physics and extensive experience in the field of critical compilation of atomic spectral data. Applicants should also have demonstrated experience with high-level programming for database client-server applications, including knowledge of Fortran, Visual Basic, C++, Perl, Java, Javascript, and Pascal. Experience with html, XML, and SQL programming is also required. The position is for a ZP-1310-IV Physicist. Salary range is $79,397 to $121,967. The vacancy announcement may be viewed at **website: http://www.usajobs.opm.gov,** number PHY-2007-0004. Apply directly to the vacancy announcement on USAJOBS. Incomplete applications will not be considered. *NIST is part of the U.S. federal government and U.S. citizenship is required. The Department of Commerce is an Equal Opportunity Employer.*

STAFF SCIENTIST. Boston University Medical Center is recruiting an established **BASIC BIOMEDICAL INVESTIGATOR** with extensive expertise in the area of intestinal mucosal immunology. Candidate must have an M.D. or Ph.D. degree or equivalent, and experience in the area of inflammatory bowel diseases is highly desirable. Faculty appointment commensurate with level of expertise and proven proficiency. Interested candidates should forward their curriculum vitae to: **M. Michael Wolfe, M.D., Chief, Section of Gastroenterology, Boston University Medical Center, 650 Albany Street, X 504, Boston, MA 02118.** *An Equal Opportunity Employer.*

POSITIONS OPEN

USDA ARS Agricultural Research Service

COMPUTATIONAL BIOLOGIST
USDA/Agricultural Research Service
Corn Insects and Crop Genetics Research Unit
Ames, Iowa

The Corn Insects and Crop Genetics Research Unit conducts research on the biology of improving grain and forage crops. The unit is seeking a Computational Biologist to fill a position at MaizeGDB, the MaizeGenetics and Genomics Database **(website: http://www.maizegdb.org).** This position is housed on the Iowa State University campus in Ames, Iowa. The successful candidate will work in collaboration with both laboratory scientists and computational biologists to develop new computational and analytical methods, create unique genomic data storage solutions and views, and serve as a technical resource and advisor to the MaizeGDB project.

A Ph.D. in bioinformatics, computational biology, genetics, or related discipline appropriate to the position is required. Experience in interdisciplinary scientific computing, genomic data analysis, storage and presentation of genome annotations, and/or database development is highly desirable. For further information on this position contact **Dr. Carolyn J. Lawrence** at **e-mail: triffid@iastate.edu.**

Candidates must be U.S. citizens. The position will be filled at the GS-11/12 level; **ASSISTANT/ASSOCIATE PROFESSOR** equivalent, salary commensurate with experience ($52,912 to $82,446). Comprehensive benefits package includes paid annual and sick leave, life insurance, health insurance, and a federal retirement plan. Vacancy announcements and application information can be obtained from the ARS **website: http://www.afm.ars.usda.gov/divisions/hrd/.** Questions regarding application procedures can call **Lynnette Richey, telephone: 515-663-7278.** Applications in response to this ad must be postmarked by February 26, 2007, and reference vacancy announcement number ARS-X7W-0091. *The USDA/ARS is an Equal Opportunity Provider and Employer.*

FACULTY POSITIONS

FACULTY POSITION
Bioinformatics/Computational Biology
University of Nevada, Reno

The University of Nevada Reno invites applications for a tenure-track faculty position in bioinformatics at the **ASSOCIATE** or **FULL PROFESSOR** level. The successful candidate will direct the Center for Bioinformatics funded through the NIH INBRE program. The ideal candidate will be expected to develop and maintain a vigorous, innovative, state-of-the-art computational biology research program on integrative data analysis and interpretations using mathematical and statistical models in biological systems along with the development and teaching of a curriculum for bioinformatics. Possible areas of research emphasis could be systems biology, functional genomics, proteomics, metabolomics, network analysis, biostatistics or comparative genomics. Applicants should have a record of productive, grant-supported research. Reno, Nevada, is on the eastern flank of the Sierra Nevada range, offers outstanding opportunities for outdoor recreation, and was recently rated one of the best small cities in the United States for overall quality of life.

Applicants should send curriculum vitae, statement of research plans, statement of teaching philosophy and bioinformatics curriculum goals electronically to: **website: http://www.unrsearch.com** and three letters of recommendation to: **Barbara Neyses, Search Coordinator, Department of Biochemistry, School of Medicine/200, University of Nevada, Reno, NV 89557.** The complete position announcement and requirements can be viewed at **website: http://jobs.unr.edu.**

Equal Employment Opportunity/Affirmative Action Employer.

FACULTY POSITIONS

EVOLUTIONARY BIOLOGIST, University of North Texas (UNT), Denton, Texas. The Department of Biological Sciences **(website: http://www.biol.unt.edu)** invites applications for a tenure-track **ASSISTANT/ASSOCIATE PROFESSOR** position in evolutionary biology starting September 1, 2007. Successful candidates will be expected to contribute to a strong research program and participate in instruction at the undergraduate and graduate levels (M.S./Ph.D.). Candidates with demonstrated research excellence in addressing evolutionary questions in microbial, plant, or animal systems, especially as related to the environmental sciences, are encouraged to apply. Excellent research facilities, competitive salary, and startup funds are available. Located in the Dallas-Fort Worth metropolitan area and about 30 minutes from the Dallas-Fort Worth International airport, UNT has over 33,000 students. Applicants should send a cover letter that addresses the above requirements as well as curriculum vitae, a statement of teaching goals, a statement of research interests and goals, contact information for at least three references, and selected reprints. All application materials should be addressed to: **Dr. T. W. La Point, Chair, Evolutionary Biologist Search Committee, Department of Biological Sciences, P.O. Box 310559, University of North Texas, Denton, TX 76203-0559.** Review of applications will begin February 16, 2007, and will remain open until filled.

The University of North Texas is an Equal Opportunity Affirmative Action Institution committed to diversity in its employment and educational programs, thereby creating a welcoming environment for everyone.

PROFESSOR OF THE PRACTICE

The Department of Ecology and Evolutionary Biology, Tulane University, invites applications for a full-time teaching position. Professors of the Practice are appointed for renewable three-year terms, which include benefits but do not lead to tenure. Candidates must hold a Ph.D. degree and should have teaching experience at the college level. We seek an individual with demonstrated expertise in one or more areas of ecology, evolution, and organismal biology as well as a commitment to excellence in undergraduate instruction, the advancement of science literacy, and the scholarship of teaching and learning. For more details see **website: http://www.tulane.edu/~ebio/News/profprac.htm.** Send curriculum vitae, description of scholarly and teaching interests and experience, selected publications, statement of teaching philosophy, and the names and addresses of three references to: **PoP Search, Department of Ecology and Evolutionary Biology, 310 Dinwiddie Hall, Tulane University, New Orleans, LA 70118-5698.** Review of applications will begin March 1, 2007, and the search will remain open until the position is filled. *Tulane University is an Affirmative Action/Equal Employment Opportunity Employer.*

POSITIONS OPEN

POSTDOCTORAL FELLOW POSITIONS

Postdoctoral Positions are available immediately in the Institute of Biotechnology/Department of Molecular Medicine at the University of Texas Health Science Center at San Antonio. The research involves the use of molecular biology and mouse genetics to study the impacts of gene regulation, obesity, and hormone actions on the development of breast cancer. The successful candidates should hold a Ph.D. degree in biochemistry, molecular biology, or other related fields, with a record of creativity and scientific productivity. Working experience in mouse genetics is preferred but not absolutely required. Please provide curriculum vitae, a brief summary of research experience, and the names and contact information of three references to: **Dr. Rong Li, e-mail: lir3@uthscsa.edu** or **Yanfen Hu, e-mail: huy3@uthscsa.edu.**

The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer. All postdoctoral appointments are designated as security-sensitive positions.

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